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The effects of Prism Adaptation on Unilateral Spatial Neglect

Ph.D Thesis

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June 2009

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I would like to dedicate this thesis to

Dr Alan Beaton

and to the memory of

Mr Philip Heard

Acknowledgements

Thank you to Dr Alan Beaton for inspiring my interest in neuropsychology and for being a fantastic supervisor. Thank you to Dr Rodger Weddell for always making time to help me and for whose contribution has been invaluable. Thank you to both of you for always believing in me and for being exceptional at what you do.

Thank you very much for all of the patients who took part in my research and to their husbands and wives; if it were not for them this research would not have been possible or as pleasurable.

Thank you to the technical staff at Swansea University who made this research possible, specifically Neil Carter and Tony Aldridge. Thank you to the support staff, Norma, Jackie and Bev, for being such lovely supportive people.

Thank you to my parents, Shelagh and David Fisher, for being the best parents in the world and for always going out of their way to support me. Thank you also to my twin sister, Samantha; I could not have wished for a better clone!

Thank you to Scott Bruning for being so understanding during the long write up process and for his support throughout. Thank you to my friend, Liz Rudman for her support and kindness. Thank you to Alys Jones, Amy Howells, Mia Winter, Liam McCarthy and Christopher Hunt for their support, willingness to help and for making me laugh.

Abstract

This thesis concerns the syndrome of visual unilateral spatial neglect (USN). Pisella and Mattingley (2004) argue that two of the core deficits associated with USN, the ipsilesional reaction time (RT) bias (thought to reflect the ipsilesional attention bias) and the ipsilesional detection bias, may have distinct neural substrates and thus may dissociate. In the research reported in this thesis, the ‘dissociation hypothesis’ was explored in a single patient (JH). JH was impaired at detecting contralesional targets on the visual search task in near space but her far space contralesional target detection was comparable with a healthy control group. However, despite showing ‘normal’ target detection in far space her far space RTs were significantly slower to detect contralesional targets relative to ipsilesional targets. In fact her RT data was comparable with the far space RT data of 6 patients with USN and was significantly different than that of 10 healthy control participants. This data suggests that the ipsilesional RT and the ipsilesional detection bias can dissociate and may be underpinned by distinct neural processes. The patient was then given PA training. Overall, the analysis showed that the ipsilesional detection bias was ameliorated after PA but the ipsilesional RT gradient remained unchanged.

A group study was carried out to explore whether PA ameliorated both the ipsilesional detection bias and the ipsilesional RT bias, (due to the limitations of the case study approach). As research has already shown that PA improves contralesional target detection (Rossetti et al., 1998; Frassinetti et al., 2002) the experiments asked whether increased target detection after PA is accompanied by a normalisation of the ipsilesional RT bias on a visual search task, as would be predicted if PA ameliorated USN by facilitating a redistribution of spatial attention (Rode, 2003; and Pisella, 1999). The findings showed that increased contralesional target detection was not accompanied by a normalisation of the ipsilesional RT gradient. This suggests that a) the ipsilesional detection and the ipsilesional RT bias are not intrinsically related and b) that PA does not facilitate a redistribution of spatial attention. It was argued that PA improves target detection by ameliorating the remapping deficit associated with PA (Pisella and Mattingley, 2004) without ameliorating the ipsilesional attentional bias.

It was argued in the rationale section of this thesis that the conventional PA procedure described by Rossetti (1998) is a far space based procedure as patients adapt to the prismatic shift by pointing to objects in far space (beyond arm’s reach). However, the patients in Rossetti’s (1998) study, and subsequent studies by others, were asked to perform tasks that evaluated the effects of PA **only** in **near** space. The findings of Rossetti (1998) and others showed that ‘far PA training’ ameliorated left USN performance in near space, thereby suggesting that a common underlying mechanism involved in both near and far space processing is ameliorated by PA. A candidate for this mechanism may be the oculomotor system since research has shown that it may be involved in the detection of objects in both far and near space (Previc, 1995). Further,

the oculomotor system has been implicated as being involved in the amelioration of USN after PA training (Serino et al., 2007).

If it is the case that a mechanism common to processing of both near and far space is ameliorated by PA training, then near space training should also ameliorate USN of far space. On the other hand, there are indications in the literature that the oculomotor system is involved in processing of near and far space to different degrees, being more directly involved in processing of far than near space (Berti and Rizzolatti, 2002). There is also evidence that near and far space are processed by different neural circuits (Rizzolatti et al., 1987, 1985 and 2002). It is conceivable, therefore, that a PA training method based on processing of near space information would have a greater effect on neglect for near space than for far space. A 'near space' training procedure was therefore devised to explore this issue. Specifically, the experiments reported in Chapter 7 asked whether a 'near PA' procedure, which attempted to activate near/reaching circuits (in addition to the oculomotor system), would ameliorate USN in near and far space but to a greater degree in near space. The findings showed that 'near PA' significantly increased contralesional target detection in both near and far space with no enhanced benefit in near space.

It was evident when carrying out the group study described above that not all patients benefited from PA training. The group data was re-analysed at a single case level and the findings showed that of the 9 patients who were given PA training only 6 showed a subsequent reduction in symptoms of USN. All of the patients who responded to PA showed error reduction and after effect. Of the patients who did not respond to PA, none showed error reduction and two showed an after effect. It was concluded that error reduction and not after effect is the critical predictor of amelioration of USN symptoms after PA. A final longitudinal study explored how long the effects of PA lasted in three patients with USN who responded to PA training. The findings showed that the beneficial effects of PA were maintained for at least two years in one patient but two patients who initially benefited initially from PA lost their training gains over time.

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Chapter 1

Unilateral Spatial Neglect: A General Review

1.1) Behavioural and clinical description of unilateral spatial neglect

Unilateral spatial neglect (USN) is characterised by the inability to notice or respond to information in the contralesional side of space. Patients with USN fail to acknowledge that objects or events in the contralesional side of space exist. Right hemispheric damage to specific brain areas can result in USN for the left side of space whereas left hemispheric damage can lead to USN for the right side of space. Patients with USN often walk in to objects on the contralesional side, eat food off one side of their plates, dress or groom half of their body, read half of a page and so on. Patients with USN may act as if their trunk and head have been rotated towards the ipsilesional side of space. During testing, the patient may appear to be 'magnetically' drawn to stimuli or events on the ipsilesional side of space. Ishiai, Furukawa and Tsukagoshi (1979) examined the eye movements of USN patients and found that most scanning saccades were restricted to the ipsilesional side of space, even though these patients were able to make full ocular movements when instructed to do so. One of the most intriguing aspects of this syndrome is that the patient remains unaware of his or her deficit. Clinically, patients show a lateralised deficit on a variety of neuropsychological tests. On bedside tests for USN, patients usually miss contralesional targets on line, star and letter cancellation tasks. Their bisection performance deviates ipsilesionally on line bisection tasks and when asked to copy pictures patients usually omit contralesional details.

1.2) Functional outcome

The presence of USN is one of the best single predictors of poor functional outcome after a stroke (Denes et al., 1982; Kinsella and Ford, 1985). Jehkonen (2000) showed that despite the fact that speech and language, memory, and other cognitive abilities may be spared in patients with USN, the prognosis for recovery of independent function in patients with persisting USN is worse than in those with other, seemingly more

disabling, deficits. Denes et al. (1982) reported that even global aphasia and right hemiparesis may not have as great an effect on the ability to become independent.

1.3) Sensory and motor deficits

USN cannot be attributed to a disturbance of primary sensory or primary motor inputs (Vallar, 1998). Although it is common to see patients with USN who do have primary sensory or motor disturbances, USN and sensory-motor deficits do not seem to be related. USN patients have been reported who have no damage to primary sensory or motor areas of the brain (Behrmann et al., 1997; Husain et al., 2001, Halligan, Marshall and Wade, 1990). Many brain damaged patients have hemianopia after destruction of the striate visual cortex or hemiplegia after destruction of the corticospinal pathways but do not show visual or motor USN. Rather, USN is associated with lesions affecting the inferior parietal lobe and interconnected regions (Vallar and Perani, 1986; Kerkho., 1999a).

1.4) Right hemispheric dominance for spatial attention

In humans, but not monkeys, left USN is far more frequent and long lasting than right USN (De Renzi, 1997). Some researchers have argued that this apparent asymmetry is due to subject selection; left hemisphere patients may have dysphasia which could impair comprehension and their ability to perform tests of USN. However, this issue has been addressed by studies involving unselected samples that have used very simple tests to assess USN. These studies have supported the view that USN is more common and more severe after right than left hemispheric brain damage (Bisiach et al., 1984; Fullerton, McSherry and Stout, 1986). By contrast, studies that have reported no significant difference in the frequency of USN between left and right brain damaged patients have usually involved patients with tumours (Albert, 1973; Ogden, 1985), as opposed to stroke patients who have participated in the majority of USN studies. For example, Ogden (1985) reported that the incidence of right and left USN was equivalent in tumour patients but right USN tended to be less severe than left USN. However, Vallar and Perani (1987) argue that patients with tumours, unlike stroke patients, have additional complications such as oedema, compression and the infiltration of

neighbouring brain regions. Anderson, Damasio and Tranel (1990) reported that tumour patients and stroke patients show major differences in their neuropsychological impairments

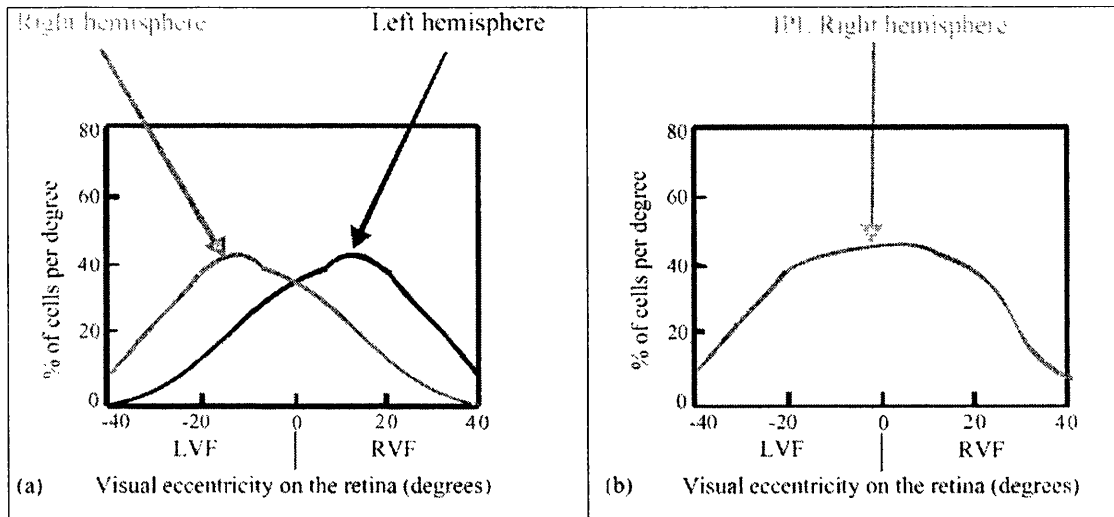
Marshall, Halligan and Wade (1989) used a battery of six USN tests in a group of patients who were, on average, two months post-stroke. The findings showed that 48% of the right hemisphere group had USN compared to 15% of left hemispheric patients. It may be that time is an important factor when considering the frequency of USN after right compared to left hemisphere strokes. Stone et al. (1991) discovered that three days after a stroke, the incidence of USN after right and left hemisphere damage was the same, but after three months the relative incidence of USN was far greater for the right hemisphere group. If the right and left hemispheres of human patients are temporally inactivated by sodium amytal injections to the carotid artery, only right hemisphere inactivation leads to a transient visual USN (Spiers et al., 1990). Further, Meador et al. (1988) demonstrated tactile extinction after right, but not left, sodium amytal injections. Thus, overall, the evidence suggests that the incidence of left USN is higher than right USN, particularly at times later than three months post- stroke.

Several theories suggest that the left hemisphere allocates attention to the right side of space whereas the right hemisphere allocates attention to both the left and the right side of space (Mesulam, 1981; Kinsbourne, 1987). If so, a left hemispheric lesion would not cause right USN as the right hemisphere would still be able to allocate attention to both sides of space. However, a right hemispheric lesion may trigger severe left USN as the left hemisphere only allocates attention to the right side of space (Heilman and Van den Abell, 1980; Kinsbourne, 1987). Mesulam (1999) incorporates and extends these theories suggesting that the left hemisphere: a) attributes salience to the right side of events; b) coordinates the distribution of attention within the right side of space; c) shifts attention mainly in a contraversive rightward direction. The right hemisphere: a) attributes salience to both sides of events; b) coordinates the distribution of attention within the right and left side of space; c) shifts attention in a contraversive and ipsiversive direction (with a slight contraversive bias). He further suggests that there are

more neurones in the right hemisphere dedicated to spatial attention and therefore the right hemisphere is more likely to be activated by spatial attentional tasks.

Pouget and Driver (2000) showed that in the monkey parietal lobes the number of neurones representing the visual environment in each hemisphere can be represented by an asymmetric curve. The majority of these neurones have been shown to respond to visual stimuli located fifteen degrees within the contralateral side of space and a decreasing number of neurones respond to visual targets from this optimal point to the extreme ipsilateral position in space. It is pertinent to note that in monkey VIP there are neurones in each hemisphere that represent the ipsilateral side of space (although these are far fewer than the number representing contralateral space). However, it has been argued that in humans the right parietal lobe is more specialised for spatial processes than is the left hemisphere. As discussed previously, it has been proposed that the right hemisphere in humans is responsible for allocating attention to both the left and the right visual fields whereas the left hemisphere allocates attentional resources to the right side of space only. Imaging data suggests that this asymmetry relies on a bilateral representation of space specifically in the right parietal lobule. In humans, a bell-shaped curve can represent the way in which neurones in the right hemisphere respond to visual information, unlike the mirror image asymmetric representations of the right and left monkey brain. Figure 1.1 shows that the number of neurones representing the visual environment in each monkey hemisphere is represented by an asymmetric curve. The number of neurones representing the visual environment in the left human hemisphere is also represented by an asymmetric curve. However, because the right hemisphere in humans has become specialised for visual attention, the neural representation of the visual environment in the right hemisphere is thought to be represented by a bell-shaped (symmetric) curve. Figure 1.1 shows the spatial distribution of the receptive fields of parietal cortex neurones for the right and the left hemisphere separately [figure taken from Pisella and Mattingley's (2004) paper].

Figure 1.1 shows the spatial distribution of receptive fields of neurones of the parietal cortex for the right and the left hemisphere separately.



Damage to specific areas in the right or left monkey parietal lobes creates a gradient of detection impairment so far as the performance becomes increasingly worse for stimulus events occurring increasingly further towards the contralesional side of space (Smania et al., 1998). In humans, one would expect to see the same gradient of impairment after damage to the right parietal lobule as patients would be left with the steep ‘asymmetric’ gradient of the left hemisphere. For example, Butler et al. (2009) showed that patients with left USN showed a gradient of detection performance on a visual search program administered in both near and far space. Overall the left USN patients showed a decrease in the proportion of target detections as they progressed from right-to-left in both near and far space. This would not be the case after left hemisphere damage since attention would be allocated to both the right and left visual fields. As left USN is much more frequent than right USN in humans, the remainder of this discussion will focus on left USN unless explicitly stated otherwise.

1.5) Dissociations and double dissociations within the USN syndrome

USN is a heterogeneous disorder and has been shown to fractionate into a number of discrete syndromes. Each fractionation has been shown to occur in isolation within a

single patient. These fractionations are very informative and offer insight into normal brain function. One is able to use single and double dissociations between patients to make predictions about brain function and modularity. The review will briefly discuss the fractionations and reported double dissociations, focusing in particular on the fractionation that is relevant to the work reported in this thesis: the fractionation between near and far space.

Coslett (1997) reported a double dissociation between USN for visual and mental imagery; this suggests that visual and mental imagery do not rely on the same neural substrates. Young et al. (1990) claimed that their patient showed USN for face stimuli but not for other types of visual stimuli. USN for reading, referred to as neglect dyslexia, has been reported in isolation from (or independent of) USN on other visual tasks (Baxter and Warrington, 1983; Patterson and Wilson (1990); Riddoch, Humphreys, Cleton and Frey (1990). Motor neglect is a condition in which patients fail to use the contralesional limb spontaneously which cannot be accounted for by primary motor deficits. Patients have been reported with motor neglect, in the absence of USN on other visual tasks (Laplane and Degos, 1983; Valenstein and Heilman, 1981). Conversely, many patients have been reported who had USN on visual tasks but showed no evidence of motor neglect (Liu, Bolton, Price and Weintraub, 1992).

Gainotti, D'Erme, Monteleone and Silveri (1986) observed that when their patient was asked to copy a complex drawing, he ignored the left part of each object in the visual array, instead of ignoring the left part of the visual array as is most commonly observed in USN patients. This finding was supported and extended by a study carried out by Driver and Halligan (1991); their patient had a tendency to neglect the left side of objects even when they were rotated and the left part of the stimulus was on the right side of the display. This has been referred to as object based neglect. Although USN is most commonly reported across the X axis of space, it has also been reported across the Y axis. This is often referred to as vertical or altitudinal neglect. Patients with this disorder neglect information that occurs in the upper or the lower quadrant of space (Rapsack, Cimino and Heilman 1988).

1.5.1) The dissociation between near and far space.

USN has also been shown to dissociate as a function of position across the Z axis. Dissociations have been reported for personal, near (peripersonal) and far (extrapersonal) space. Personal space is the space of the body surface; this includes the space where one can perceive touch, the space in which one grooms or scratches. Patients with personal neglect often fail to groom or shave half their face, dress half their body or to notice the position of their limbs and use them appropriately even in the absence of motor weakness. Near space, also referred to as peripersonal or reaching space, is the space within arm's reach, the space in which one writes or picks up a cup. Far space, often referred to as extrapersonal space, is the section of space beyond arm's reach, the space in which objects cannot be reached, such as the space one views in the cinema or when playing darts¹.

1.5.2) The dissociation between near and far space: evidence for distinct neural circuits underlying the representation of visual information in near and far space in the monkey brain.

It had previously been thought that space was coded in the brain by a multipurpose space centre located in the parietal lobes and that object related actions were executed only when the spatial position of the objects to be acted upon were localized in space. This view suggests that objects are localized before action plans are generated. However, Berti and Rizzolatti (2002) point out that if the parietal lobe were a multipurpose space centre its inputs would be similar to that of a sorting station that receives convergent inputs from a series of areas and sends divergent outputs to a series of other areas (Berti and Rizzolatti; 2002). In contrast, the parietal lobe is anatomically segregated into a number of separate regions and each of these regions has segregated connections with the occipital lobe, the frontal lobe and the subcortex (Petrides and Pandya, 1984; Cavada and Goldman-Rakic; 1989; Anderson et al. 1990, 1997). Berti and Rizzolatti (2002) suggest that the neuroanatomical properties of the parietal lobes (a series of circuits working in parallel) are not compatible with the notion of a single multipurpose map. In

¹ Different theories have proposed that space may be divided into more than the three sections outlined here. These theories will be discussed elsewhere in this thesis.

addition, much work has shown that the anatomically segregated areas of the parietal lobe correspond to functional segregation. Snyder et al. (1997) Rizzolatti et al. (1998) and Colby and Goldberg (1999) demonstrated that various parietal areas have specific functional properties, with each area using sensory information for different motor purposes.

The ocular motor (oculomotor) circuit is formed by the lateral intraparietal area (LIP) and the frontal eye field (FEF). The reaching circuit is formed by the ventral intraparietal area (VIP) and the premotor area (F4). Neurones in both areas respond to visual stimuli and discharge during movement. Aside from these common features the neurones in each of these two circuits have very different properties. In the oculomotor circuit neurones respond to visual stimuli whatever the distance of the stimuli from these neurones. The neurones in this circuit have receptive fields that code information in retinal coordinates and the motor properties of these neurones are exclusively related to eye movements (Anderson et al; 1997). The reaching circuit comprises mostly of bimodal neurones which respond to tactile and visual stimuli. The neurones in this circuit have receptive fields coded in body part coordinates and their motor activity is related to the movement of body parts. Further, in order to activate the neurones in the reaching circuit the visual stimuli should be presented within the reach of the body part (Gentilucci et al, 1983; 1988; Granziano and Gross, 1995). The important point is that these two circuits code space in very different ways. In the oculomotor circuit, spatial information derives from neurones whose receptive fields are coded in retinal coordinates. Zipser and Anderson (1988) showed that the position of an object is reconstructed by computing the position of the object on the retina and the position of the eye in the orbit. In the reaching circuit, space is coded in egocentric co-ordinates. Receptive fields of neurones in the reaching circuit are anchored to the body parts to which they correspond regardless of eye or body part position (Gentilucci et al, 1983; 1988; Granziano and Gross, 1995).

In addition to oculomotor deficits, lesions to the oculomotor circuit (LIP-FEF) in monkeys produce a preference for ipsilesional stimuli and in cases of large lesions to the

FEF, unawareness for the contralesional side of space, which is particularly marked in far space relative to near space. In contrast, lesions to monkey reaching circuits (VIP-F4) produce unawareness of contralesional stimuli which is especially severe when stimuli are presented near the animal's face and body. In summary, neurophysiological studies in the monkey support the view that there are several areas for space representation.

1.5.3) The dissociation between near and far space in humans.

Brain (1941) reported a case of a patient with right hemisphere glioblastoma: the patient was impaired in pointing to objects in near space but not in far space. Similarly, Marshall and Halligan (1991) reported a patient who demonstrated a severe left USN on a line bisection tasks in near space, but did not show USN when tested in the same way in far space. They reported the opposite pattern in a haematoma patient who showed USN for far space but not near space on a line bisection task.

Cowey, Small and Ellis (1994) examined thirteen patients with left USN. They found that five of the patients performed more poorly on a line bisection task presented in far space than on a comparable line bisection task in near space. They also reported that neglect performance increased as viewing distance increased, which is difficult to explain in terms of lesion sites and merits further investigation. However, Berti and Rizzolatti (2003) point out that only one of the patients in the Cowey et al. (1990) study presented with a smooth gradient going from near to far distances. All of the other patients showed an abrupt change, although at different distances.

In contrast to a right hemisphere control group who did not have USN and a healthy control group, Bulter (2004) reported that patients with USN showed lateral gradients of increasing target detection from left to right in both near and far space. Bulter et al. (2004) also reported a double dissociation in differences in the slope of target detection gradients between near and far space on a visual search and detection task; suggesting that the severity of USN differed between near and far space. Lesion analysis showed that near USN was associated with dorsal stream damage whereas far USN was associated with ventral stream damage.

Guariglia and Antonucci (1992) demonstrated that patients can show USN for personal space without showing USN for near space. Bisiach, Perani, Vallar and Berti (1986) demonstrated that USN for personal space can occur without USN for near space and that USN for near space can occur without USN for personal space.

The reported double dissociation suggests that the brain areas representing near and far space in humans may have different anatomical loci. However, in contrast to the above studies an early study by Pizzamiglio et al. (1989) failed to find evidence for a near and far distinction in man. Pizzamiglio et al. (1989) gave five patients with right brain damage a modified version of the Wundt-Jastrow illusion. In this illusion two areas of the same extent and shape are arranged such that healthy controls indicate that one of the areas is longer than the other. When the orientation of the stimuli was subjectively perceived as directed to the left side, the patients were not affected by the illusion and gave responses opposite to that of healthy controls. Pizzamiglio et al. (1989) presented the illusion to USN patients in near and far space and found that performance did not differ as a function of position of the stimuli on the Z axis. They suggested that the strong association between performance in near and far space suggested a unitary system in which space is coded in the human brain. As Pizzamiglio et al. (1989) failed to find differential performance in near relative to far space, it was suggested by Pitzalis et al. (2001) that the findings of Marshall and Halligan (1991) (showing a dissociation between near and far space) were a result of the involvement of a motor component in their line bisection task. To explore this hypothesis Pitzalis et al. (2001) carried another experiment looking for a dissociation between near and far space using a perceptual task. The authors demonstrated a dissociation between near and far space using this purely perceptual task. Berti and Rizzolatti (2002) argue that these data further support the idea that within a given space region, the activity of the same brain circuits subserves both perceptual and visuomotor tasks.

Weiss et al. (2000) conducted a study of horizontal line bisection and dot pointing in healthy volunteers using PET. Volunteers were asked to bisect lines or point to dots in either near or far space, using a laser pen. Participants performing the pointing and

bisection task in 'near' space showed neural activity in the left dorsal occipital cortex, left intraparietal cortex, left ventral premotor cortex and left thalamus. Participants' performance on the pointing and bisection task in 'far' space showed activation of the ventral occipital cortex bilaterally and the right medial temporal cortex. Weiss et al. (2000) argue that the data provided support for the double dissociations reported between near space and far space, and that attending to and acting in near space differentially engages dorsal visuomotor processing areas, whereas attending to and acting in far space differentially engages ventral visuoperceptual processing areas (even when the motor components of the tasks are identical in reaching and far space). One puzzling aspect of the findings is that tasks performed in near space primarily activated the left hemisphere. One must therefore ask why lesions to the right hemisphere induce neglect for near space and why it is that right hemispheric damage can cause USN for near space but not for far space as reported by Marshall and Halligan (1991). One possibility is that the left hemisphere activation observed during near space actions was due to the demand for more hand activity in the near space task than the far space task (the tasks were performed by the right hand and hence would cause increased left hemispheric activity). In the study by Weiss et al. (2000) two different motor tasks were performed in near and far space: manual line bisection and dot pointing. The design does not allow one to distinguish whether the differential neural mechanisms observed were related to computing the relevant spatial positions or acting on the result of those computations when the stimulus was in near versus far space. To rectify this problem Weiss et al. (2003) carried out another study in which they investigated whether action and perception elicited distinct cerebral representations in near and far space. Regional cerebral blood flow (rCBF) was measured in healthy controls who were asked to perform manual line bisection (action) and make line bisection judgements (perception). The stimuli were presented in either near or far space. The results, in agreement with their previous findings (Weiss et al., 2000), showed that performance in near space draws differentially on the dorsal visuomotor processing stream and performance in far space draws differentially on the ventral visuoperceptual processing stream. Importantly, the findings also showed differential neural mechanisms are implicated when processing stimuli in near and far space irrespective of the particular task

demands; there was no significant interaction between brain regions activated during manual line bisection or line bisection judgments and the spatial region of presentation (near versus far).

1.5.4) Theoretical models about how the 3D world around us can be partitioned.

Previc's (1990a) neuropsychological model suggested two major 3D realms: a peripersonal one (immediately surrounding the person) that is important in visual reaching and manipulation and a focal extrapersonal one (generally located at a greater distance from the person) that is important for visual search and object recognition. In this model Previc (1990a) also posited the existence of an additional extrapersonal region referred to as the ambient extrapersonal realm. This realm is important in the maintenance of spatial orientation and postural control during locomotion. In his original model and in later expanded models, Previc (1990a) proposed that a) the peripersonal visual realm extends about 30 degrees laterally to each side of the body's midline and is biased towards the lower visual field, which represents the general region of our reaching space and b) interactions within peripersonal space are mediated by the dorsal (predominantly magnocellular system) cortical pathways. In contrast, the focal extrapersonal visual realm was described as a football shaped region that, because of limited capabilities of the peripheral retina in processing detailed form information, falls off rapidly from the fixation point in both depth and eccentricity. Previc argued that its interactions were handled mainly by the ventral (predominantly parvocellular system) cortical visual pathways. The ambient extrapersonal realm was described as occupying the most laterally eccentric and distant portion of the visual world in accordance with the evidence suggesting a critical role of the distant, peripheral visual field in the maintenance of spatial orientation and postural control (Dichgans and Brandt, 1978; Previc and Neel, 1995).

A different neuropsychological model of 3D space was proposed by Rizzolatti and Camarda, (1987) and Rizzolatti et al. (1985). Based on numerous animal lesion studies (some of which have been reviewed above) Rizzolatti et al. (1987, 1985 and 2002) highlighted three important regions of 3D space: a personal space in which oral-tactile

interactions occur, a peripersonal (distant reaching) space, and a far (oculomotor) space. Rizzolatti et al. (1987, 1985 and 2002) argue that parietal area 7b and postarcuate frontal area 6 are highly involved in personal interactions. Parietal areas 7a and 7b and frontal areas 6 and 8 all combine to mediate distant peripersonal interactions. Frontal area 8 and parietal area 7a are highly involved in the exploration of far space.

A third model by Grusser (1983) divides the external world into four major components: grasping space, near-distant action space, far-distant action space, and the visual background. Grusser (1983) further divided grasping space into several subregions: oral grasping space; manual grasping space, and instrument grasping space. Previc (1995) partitions space into four major zones of interaction. The zones are referred to in his model as peripersonal space, focal extrapersonal space, action extrapersonal space and ambient extrapersonal space.

1.5.5) Why is there differential coding of near and far space in the brain?

Berti and Rizzolatti (2002) suggest that space representation is not a 'primary' brain function, instead they argue that space representation is derived from activity of circuits that are involved in organising actions with different effectors (such as an arm reaching movement or an eye movement) towards a specific object location. They argue that all these circuits compute space but that this computation is different depending on the different effectors. Thus in contrast to the view that space representation is 'sensorial' and that the link with the motor system is secondary, Rizzolatti et al. (1997) argue that space is primarily 'motor' and is constructed through action. They suggest that 'once the motor representation of space is consolidated, it is matched with sensory information that enriches it and gives the introspective sensorial idea of perception of space that we all share' (Berti and Rizzolatti, 2002 page 125).

The evidence presented in this review thus far demonstrated that USN is a multifaceted disorder that can fractionate in many different ways. This review will now explore the major theories of USN.

1.6) Major theories of USN

1.6.1) Posner: impaired disengagement of attention

Posner et al. (1984) proposed that there are three components of visual attention. First, there is the ability to engage visual attention. Second, there is the ability to disengage visual attention and thirdly, there is the ability to shift attention to a new target. Posner et al. (1984) argued that patients with USN had no problem with the engagement of attention but that USN is caused by the inability to disengage attention from ipsilesional targets. This marked impairment of disengagement did not occur when patients had to disengage from left-sided targets in order to engage right sided targets. Posner (1984) argued that right parietal patients had difficulty disengaging attention once it was engaged at an ipsilesional location. In short, the theory proposed by Posner et al. (1984) suggests that one of the functions of the parietal lobe is to disengage attention and that after a right hemispheric lesion patients are unable to disengage their attention from ipsilesional events.

1.6.2) Impaired orienting of attention

An alternative view is that taken by Heilman and Valenstein (1979). They suggest that USN is a consequence of decreased arousal of the damaged hemisphere. The consequence of such a unilateral decrease in arousal is thought to be the selective loss of the orientating response to the contralateral side of space.

1.6.3) Orientational bias

At the cognitive level, Kinsbourne's (1993) orientation model suggests that USN is caused by an orientation bias. He suggests that under normal circumstances the left and right hemispheres are in a state of reciprocal interaction. He argues that damage to the right hemisphere may result in the left hemisphere becoming disinhibited and largely in control biasing attention towards the right side of space. He also suggests that the right hemisphere has a more powerful orienting tendency than the left hemisphere in 'normals'. Added to this, he conceptualises attention with respect to an attentional gradient. Thus, attention is not considered to be intact in either hemisphere, but rather a lateral gradient of attention sweeps across both hemi-spaces, such that attention is biased

ipsilaterally to the absolute location of the target. Therefore, if two stimuli were presented bilaterally, one in each hemi-space, attention would be biased towards the ipsilateral stimulus. In addition, the theory argues that, even if two stimuli are presented bilaterally in the ipsilateral hemi-field, the stimulus further to the right, in the case of right brain damage, will benefit most from this attentional bias. The attentional gradient can be conceptualised in terms of the extent to which 'one stimulus rather than another captures attention and as a result, controls behaviour'. This theory relates to real or imagined objects in real or imagined space. The theory accordingly suggests that it is the relative spatial positions of objects in space that determine which has the attentional advantage, rather than the absolute position of the objects. The attentional gradient can correspond to a gravitational, viewer-centred or object-centred frame of reference, depending on the situation. Kinsbourne (1993) suggests that USN is not due to a deficit for one half of space but rather to a lateral gradient of attention across objects. He argues that at no point on the gradient is there zero probability of one detecting a target, although at various 'relative' points it may be extremely low. As a result of this orientation bias, Kinsbourne (1993) postulates that patients with USN tend to make ipsilateral saccades, and begin their search on the contralesional side of space.

In support of Kinsbourne's theory, Robertson and North (1992), showed that restoring the balance of activity between the two hemispheres by asking patients with right USN to make small repetitive movements with their left hand whilst simultaneously completing standard tests of USN improved USN symptoms. Fierro et al. (2006) and Shindo et al. (2006) showed that repetitive transcranial magnetic stimulation (rTMS) applied over the left hemisphere (thus inhibiting activity of this area) of patients with USN, improved USN symptoms. This suggests that 'damping down' the activity of the 'disinhibited' left hemisphere temporally improves symptoms of USN.

In further support of Kinsbourne's theory, Smania et al. (1998) showed that when USN patients are asked to detect targets presented at different horizontal eccentricities, their reaction times gradually increase the further the target deviates from the right. In fact, patients with USN may detect extreme ipsilesional targets faster than healthy controls.

At the neuroanatomical level, this orientation bias has been suggested to arise from the distribution of receptive fields of neurones in the parietal lobes. After right parietal damage, the distribution of receptive fields of neurones in the left hemisphere leads to a gradient of spatial representation, with most neurones responding to the ipsilesional visual field and progressively fewer representing more contralesional locations. This can be explained with reference to a defective salience map (Pisella and Mattingley, 2004).

The concept of a 'salience map' has been used by electrophysiologists to describe the type of visual representation constructed by the parietal cortex. It has been suggested that neurones in the parietal lobes code information in terms of its salience. Thus objects and their corresponding locations are assigned a value according to a salience scale based on bottom-up or top-down processes. The higher the values, the more salient the corresponding information and location are considered to be. The most salient item will subsequently be favoured for attentional processing.

Pisella and Mattingley (2004) suggest that the salience map is the first stage of visual representation and that this salience map is pathologically biased after parietal damage. The salience map would thus be the first representational level from which the pattern of attentional or ocular exploration of the visual world is derived. They proposed that at a second stage there is detailed processing via the serial application of overt or covert attention at different spatial locations within the visual scene. They argue that this application of spatial attention implements a 'winner takes all' array of space representation, where only the most salient items are selected. Pisella and Mattingley (2004) postulate that only information represented at this later stage is available for conscious report.

In summary, unilateral damage of neurones at the level of a salience map creates a gradient of impairment, with a greater proportion of neurones ready to respond to ipsilateral locations (than contralesional locations). Damaged neurones responding to input on the contralesional side of space may only elicit attenuated firing patterns and thus receive little or no attentional priority. At the second level of visual representation

attentional resources will be allocated to the ipsilateral side of space in a pathologically biased way as these ipsilesional positions will be coded as the most salient. Consequently they will receive attentional priority and will be available for conscious report. Of course, when there is no information present in the ipsilateral side of space, there will be more chance that objects in the contralesional side of space will be selected for attentional processing and these objects may then become available for conscious report. Thus the probability of a patient with USN detecting a target is never zero. This proposed deficit at the level of the salience maps (Pisella and Mattingley, 2004) may also account for the tendency of patients with USN to orient and make saccades toward the ipsilateral side of space. It may also explain why patients begin visual search and cancellation tasks on the ipsilateral extreme of the stimulus array before moving the search to more contralesional regions. Thus, when two or more targets are presented in a visual array, the critical factor would be the relative positions of the targets rather than the absolute target positions. For example, a right hemisphere damaged patient will be more likely to report the target item further to the extreme right as this target will be represented by a greater number of neurones and thus will be the most salient target in the array. If two targets are presented in the left side of space, the rightmost target would receive the most neural representation, deeming it the most salient. This target will thus be selected for attentional processing which would allow the patient to become conscious of the target.

The concept of the salience map in understanding the orientation bias observed in patients with USN seems to complement and flesh out Kinsbourne's (1993) orientational bias model of USN. It has been suggested that a potential neural correlate of the salience map is area LIP (Pisella, 2003). Gottlieb, Kunsunoki and Goldberg (1998) demonstrated that visual stimuli in their receptive fields elicited little or no response from neurones in the primate LIP unless the stimulus was behaviourally relevant or salient. Mesulam (1999) suggested that LIP neurones seem to form an internal map of extrapersonal space that is not based on the object's identity, colour, shape, and so on, but on motivational salience. This map is then used to generate 'kinetic plans' that enable one to grasp, foveate or explore salient events in space.

This review has documented the critical role of attentional deficits in understanding the pathology of USN (Mattingley and Driver, 1998). Three pathological deficits have been identified. The first: an orienting bias towards the ipsilesional side of space, reflecting a spatial gradient of attentional allocation across the visual array (Kinsbourne, 1970). The second: a deficit in disengaging attention from ipsilesional locations in order to reorient towards contralesional locations (Posner, 1982). The third: a general reduction in attentional capacity, arousal or alertness (Robertson, 1993). However, there are still some aspects of the USN syndrome that can not be adequately explained by these attentional theories (Pisella and Mattingley, 2004). Pisella and Mattingley (2004) argue that there is no coherent explanation of the lack of awareness for the contralesional side of space. Kinsbourne's (1970) orientation model of USN suggests an ipsilesional attentional bias (pathological gradient of attention) in which the most ipsilesional stimuli are favoured for attentional processing. Although this theory can explain why patients with USN orient towards ipsilesional stimuli initially, gradually moving to more contralesional stimuli, it does not explain why some contralesional stimuli are not detected at all (when viewed in unlimited time). Pisella and Mattingley (2004) suggest that lack of awareness for contralesional stimuli in USN can be explained by an additional spatial remapping deficit.

1.6.4) Remapping deficits in USN

Despite the continual movement of the eyes and attention, our perception is one of a stable, seamless world (Pisella and Mattingley, 2004). Pisella and Mattingley (2004) suggest that remapping mechanisms are necessary "in order to maintain stable and spatially relevant representations of visual stimuli across shifts of spatial attention and to update their spatial locations across ocular shifts" (pp. 186). In primary visual areas, retinotopic maps are renewed and thus overwritten at each new ocular fixation. Remapping processes operating in higher-level oculocentric visual maps of the parietal cortex ensure visual integration of these successive retinal images over time and space, by creating a constantly updated representation of stimulus locations in terms of distance and direction from the fovea. Pisella and Mattingley (2004) state that remapping

mechanisms allow us to keep a trace of the global structure of a scene to assist focal sampling at the level of local detail. Similarly when attention has selected an object in a visual scene, remapping mechanisms allow the representation of this object to be maintained when attention is directed to another part of the visual scene. They state that in the primary visual cortex, the retinal image is constructed anew at each eye fixation, overwriting information that was previously encoded. Pisella and Mattingley (2004) therefore, argue that without remapping mechanisms to maintain and relocate neural activity corresponding to these visual inputs (constructed after each eye fixation in the primary visual cortex), the general overwriting process would extend further than the level of primary retinotopic maps.

Pisella and Mattingley (2004) suggest that during exploration of a visual array the first eye movement will be oriented towards the most saliently represented location in the visual array creating a new retinotopic image. Subsequent to this first saccade remapping mechanisms are vital to ensure that the sampled scene is not fully overwritten. Remapping mechanisms are also vital to orientate the second and subsequent saccades. As a result remapping mechanisms (at the level of the parietal lobe) allow the previous representational map to be integrated into the new one at each ocular fixation (in contrast to the primary visual cortex in which there is no trace of previous ocular fixations). Corbetta, Akbudak, Conturo et al. (1998) demonstrated that visual representations are remapped after both overt (accompanied by eye movements) and covert (with visual fixation maintained) shifts of attention. Pisella and Mattingley (2004) suggest that impairment in the selection process of the information to be remapped would lead to the disappearance of relevant information from awareness across ocular or attentional shifts. Furthermore, they argue that previously sampled information must be remapped in spatial coherence with new visual inputs associated with each new ocular or attentional shift. An impairment of such refreshment and re-localisation mechanisms would lead to loss of awareness and/or mislocalisations for objects in the visual world. They suggest that a remapping deficit in the parietal cortex could account for lack of awareness of space in both USN and Balint's syndrome (Pisella and Mattingley (2004) pp 187). Pisella and Mattingley (2004) argue that patients with USN have a pathological

gradient of representation of the visual world at the level of the salience map and a remapping deficit for the information coded on the salience map. They suggest that the remapping process operates on later stages of visual perception between the 'retinotopic' salience map (the first level of visual representation) and the winner takes all array (the second level of visual representation in which information in the visual scene becomes available for conscious report).

Sapir, Hayes, Henik et al. (2004) used an Inhibition of return (IOR)² experiment to explore whether patients with parietal damage were impaired at remapping cued locations across saccades. Patients were required to make a saccade during the interval between the cue and the target presentation. After the first saccade, a healthy control group showed IOR for targets appearing at the same absolute spatial position where the cue had been presented and not for targets appearing at the location reproducing the retinal location of the cue. In contrast patients with posterior parietal damage showed IOR at the retinal location of the cue and not the absolute spatial location of the cue. The authors argue that IOR arose, in the patients, at the location where it would have occurred without an intermediate saccade, suggesting that there was an impairment in updating the position of the stimuli across saccades.

Duhamel, Goldberg, Fitzgibbon et al. (1992) asked a patient with USN after a right frontoparietal lesion to make two successive saccades in order to fixate two sequentially flashed targets each of which disappeared before the first saccade (double saccade task). When the patient was asked to make double-step saccades with targets flashed first into the right field and then into the left field she performed well. However, when asked to make the double-step saccade with targets flashed first in the left-field, she made the first saccade correctly but was unable to acquire the second target despite this requiring her to make a saccade in the ipsilesional direction. Even though this target would be coded with 'higher strength' in the salience map, suggesting that impairment in the salience map (reflected behaviourally by the RT gradient) can not adequately explain these

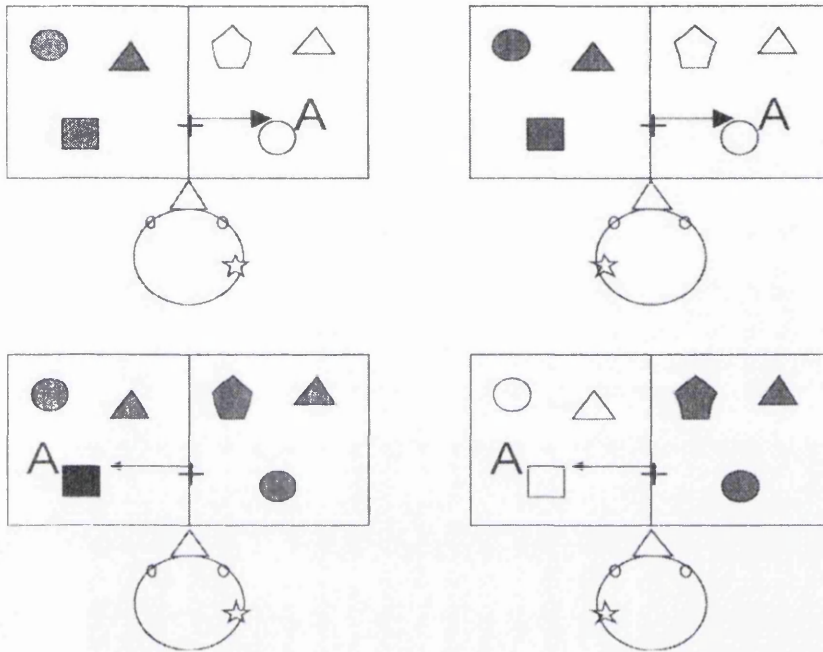
² IOR is characterised by slowed RTs to targets appearing at recently cued locations. IOR occurs when there is a sufficient time delay between cue and target presentation, at shorter stimulus onset asynchronies there is facilitation

findings. Pisella and Mattingley (2004) suggest that these findings can be explained with reference to a remapping deficit in which there is an inability to prevent the right target from being overwritten, after a left saccadic shift.

Heide, Blankenburg, Zimmermann et al. (1995) used four different types of the double-step saccade task in their experiment. Patients had damage to a number of different brain areas including the prefrontal cortex (PFC) anterior to the frontal eye fields (FEF), the right FEF, the left supplementary motor area (SMA, including the supplementary eye field) and the left and right posterior parietal cortex (PPC). Each pair of targets was located either in the same hemifield (left or right) or in different hemifields. Within hemifield trials were referred to as R-R and L-L for the two targets presented within the right or left visual field respectively. Between hemifield trials were referred to as R-L or L-R, depending on whether the right or the left target was presented first. All patients also took part in a control condition which consisted of the same double-step task, but with targets A and B presented long enough to allow the second saccade to be visually guided towards target B, obviating the need for remapping. Patients with damage to the PFC made large errors in the double step task but also in the control condition. Only patients with damage to PPC showed elevated error rates, specifically on the double-step paradigm which required remapping in at least one of the four double step tasks. The findings showed that both right and left PPC lesions caused errors in double-step saccades that involved crossing the midline (L-R and R-L between hemifield conditions). Patients with right PPC lesions, all of whom had USN, showed significant errors under conditions in which double-step saccades had to be performed within the left hemifield (L-L condition). Pisella and Mattingley (2004) argue that these results suggest that patients with right parietal lesions (and USN) are not able to execute a correct second saccade after left orientating. Specifically, they predict that damage to the right PCC (and USN) would mean that after a leftward saccade the whole salience map is overwritten, whereas after a rightward saccade only the representation of the previous left visual field in the salience map is overwritten. However, in patients with left PCC damage Pisella and Mattingley (2004) argue that, after any saccade directed towards the left or the right, only the representation of the visual field located on the side opposite

the direction of the saccade from previous fixation location is overwritten. Figure 1.2 and the text below, taken from Pisella and Mattingley's paper (2004), explains this argument.

Figure 1.2: The remapping deficit in USN.



* Visual space overwritten depending on saccade direction (arrow from fixation cross to object A) and lesion side (star). Basic model of the remapping impairments in case of parietal lesion based upon the results of Heide, Blankenburg, Zimmermann, et al. (1995). The filled shapes represent objects that will not be recombined correctly with point A in the visual maps of the parietal cortex, or that will be completely overwritten in these maps. The presence of all objects is possibly detected when the eyes are on fixation. As soon as the first saccade is oriented to point A, the objects in black will be misrepresented or will disappear from the visual representation of the parietal cortex, and thus from visual awareness (taken from Pisella and Mattingley (2004) pp191. .

Pisella and Mattingley (2004) argue that these ideas can explain why left USN is more severe than right USN. Furthermore, they claim that by postulating an additional deficit in spatial remapping, along side a deficit at the level of the salience map, they can explain aspects of USN that have not yet been explained adequately such as ipsilesional' neglect after left orienting; positive or 'productive' manifestations; spatial transposition errors; mislocalisations; revisiting behaviour during visual search and lack of awareness for objects toward the contralesional side of space (for a detailed account of the way in

which remapping mechanisms can explain these phenomena see Pisella and Mattingley, 2004).

1.6.5) The reference shift hypothesis

It has also been argued that one of the core deficits associated with USN is an alteration of the egocentric reference frame. Jeannerod et al. (1987) and Werner et al. (1953) showed that when their patients with USN were asked to point straight ahead in the dark, their subjective straight ahead pointing deviated to the right of their midline. These research findings have led to the 'reference-shift' hypothesis of USN. The hypothesis states that this orientation bias is due to an 'illusory' rotation of the egocentric reference frame. The hypothesis suggests that this orientation bias, in which patients seem to be mentally rotated ipsilesionally relative to the midline, constitutes the core of the USN syndrome.

1.6.6) Non-spatially lateralised deficits and USN

Although the defining symptom of USN is a difficulty in attending to the contralesional side of space a number of deficits have been associated with USN that are not more pronounced for one side of space than the other. These non-spatially lateralised deficits include impaired sustained attention (Roberston, Manly and Beschin et al. 1997), impaired working memory (Husain, Mannan, Hodgson, 2001) and a local processing bias (Marshall and Halligan, 1995). These non-spatially lateralised deficits are not specific to USN but research has shown that they increase the severity of USN and reduce the probability of recovery (Husain and Rorden, 2003).

1.7) Conclusions: USN is characterised by the inability to notice or respond to information in the contralesional side of space. The presence of USN is one of the best single predictors of poor functional outcome after a stroke. USN cannot be attributed to a disturbance of primary sensory or primary motor inputs. USN has been shown to fractionate into a number of discrete syndromes. Each fractionation has been shown to occur in isolation within a single patient. Main theories of USN suggest that this disorder may be associated with at least three pathological deficits in attention (an

orienting bias, a disengagement deficit and a general reduction in attentional capacity) as well a deficit in spatial remapping and an alteration in the egocentric reference frame. Other non-spatially lateralised deficits can serve to exacerbate USN and reduce the likelihood of recovery.

Chapter 2

Prism Adaptation as a Tool for Rehabilitating Spatial Neglect: A Review of the Literature

There have been many attempts to develop successful treatments for USN at both the behavioural and pharmacological level (Robertson et al., 1993). Of the interventions in use, vestibular stimulation (Rubens, 1985) has relatively short-lived effects. Attention retraining requires hours of intensive therapy (Ladavas et al., 1994) and limb activation is only appropriate for certain patients (Robertson et al., 1992). Thus, the development of an effective, practical treatment of USN would be very beneficial for patients as well as reducing the burden on the therapists and caregivers. This review will now explore the treatment approaches to USN, in particular prism adaptation (PA).

2.1) Bottom-up and top-down approaches to rehabilitation

The aim of rehabilitation in USN is to reduce the spatial bias that is characteristic of the syndrome as well as improving the patient's awareness of their deficit. Rehabilitation approaches to USN can be based either on top-down or bottom-up mechanisms. Top-down type approaches attempt to train patients to scan the affected side of space (Pizzamiglio et al., 1992; Ladavas et al., 1994). These approaches try to make the patient explicitly aware of their deficit and to reacquire the ability to voluntarily direct and maintain attention to the contralesional side of space. Thus top-down approaches aim to improve the spatial bias characteristic of USN by acting on the patient's awareness of the deficit, at the highest cognitive level.

Bottom-up mechanisms, by contrast, do not require the patient to be conscious of their impairment. Bottom-up approaches are physiological approaches aimed at modifying the sensory-motor level by passive sensory manipulation or visuomotor adaptation which bypasses the central awareness deficit and directly influences the highest cognitive levels of space and action representation (Rodes et al., 2006). Bottom-up approaches include vestibular stimulation (putting iced water in the contralesional ear or warm water

in the ipsilesional ear); optokinetic stimulation (in which a leftward moving background is used to direct the patient's attention automatically to the contralesional side of space); and proprioceptive stimulation (in which the contralesional limb is actively or passively moved). Bottom-up approaches also include transcutaneous mechanical vibration (mechanical vibrations and electric stimulations are applied to contralesional neck muscles) and transcranial magnetic stimulation (a magnetic field created over the cortex {PPC} induces an electric current in the cortex; this temporarily disrupts the functioning of neurons in the intact hemisphere, supposedly creating equilibrium between the two hemispheres). However, Frassinetti et al. (2002) point out that many of the studies exploring these techniques use only a single application and thus the effects of these sensory manipulations have so far been transient.

2.2) Prism adaptation

Prism adaptation (PA) is a technique that has been used for about a century to investigate the plasticity of sensory-motor correspondences. Research has shown that adaptation to a visual distortion can stimulate neural structures responsible for the transformation of sensorimotor coordinates. Recently, this technique has been used to rehabilitate patients with USN. However, before discussing the application of this technique to the rehabilitation of USN, it is necessary to explain the adaptation procedure and its effects in healthy volunteers.

Research has looked at the effects of prisms that reverse the upper and lower portions of space or the left and right visual fields. Sekiyana et al. (2000) have shown that people can adapt to these changes within a few days. However, these prisms cause a severe visual field cut producing uncomfortable effects for several days. A less severe type of prism simply displaces the visual field to the right or to the left (by a given amount). In these studies, the prism lenses are fitted to a pair of glasses. This technique has been shown to produce significant effects on the reaching behaviour of healthy participants. Adaptation can be obtained more quickly than with the more severe manipulations (minutes rather than days). The visual field shift alters the perceived locations of objects. The typical PA procedure is outlined below.

2.2.1) Typical PA procedure

In the exposure phase of PA, the participant is asked to put on the prismatic glasses and point to various locations in space. The altered sensory input induces a misalignment between sensory and motor space and therefore the visuo-motor behaviour generated is misdirected in space (Morris et al., 2004). If a participant is asked to point towards an object whilst wearing prismatic glasses that shifted the visual field to the right, the participant points towards the right of the actual object. This promotes a relatively abrupt reduction of the lateral pointing error as the participant strategically attempts to correct the error (strategic component of PA). The participant then typically shows a more gradual reduction of the terminal pointing error (error reduction) and after repeated attempts to point to the object achieves accuracy (this has been referred to in the literature as 'true adaptation' or 'realignment'). Pisella, Rode and Farne (2006) suggest that the strategic component of adaptation is at work for only a short period of time whereas 'true adaptation' (or realignment) develops more gradually.

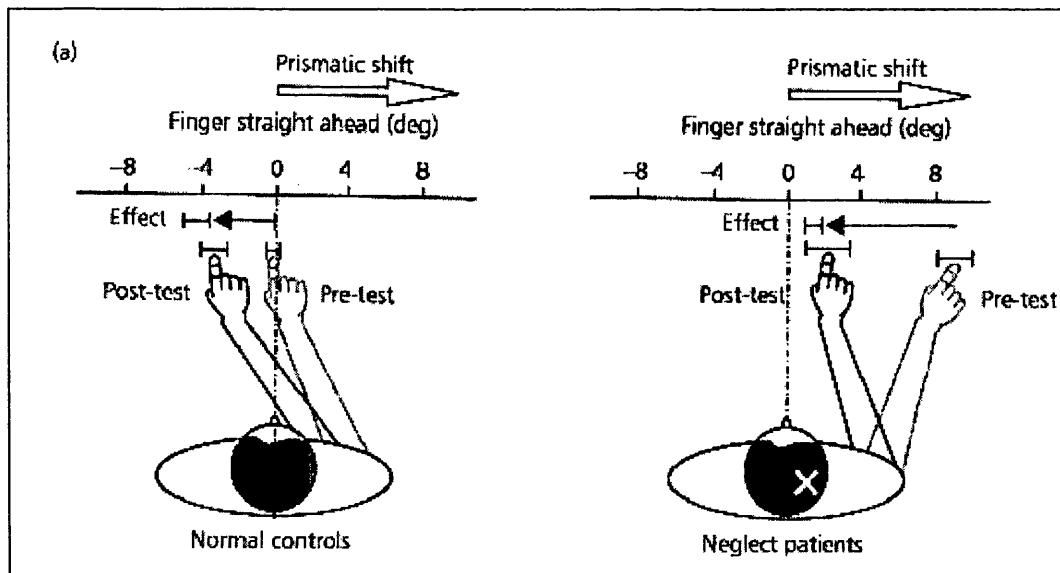
In the post exposure phase of PA, the participants are asked to remove the prismatic glasses and point to a series of visual objects. Participants again misdirect visuomotor responses, this time in the opposite direction to that of visual displacement. This is known as the after-effect. This after-effect is thought to reflect the plasticity of coordinate transformations involved in multisensory and sensorimotor integration (Rodes et al., 2006). The extent of misdirection (after-effect) is thought to provide an index of the degree of sensory and motor spatial realignment that occurred during prism exposure. After several trials, this misdirected response gradually diminishes in healthy volunteers as the motor and visual systems become realigned. The prisms used in the majority of the studies discussed below shifted the visual field ten degrees to the right.

2.2.2) Prism adaptation as a means of rehabilitating unilateral space based neglect

Rossetti, Rode, Pisella et al. (1998) were the first to investigate the effects of prism adaptation (PA) on several USN symptoms. Their patients with left USN were given prismatic glasses inducing a ten degree shift of the visual field, in order to determine whether a rightward optical deviation would ameliorate USN performance. Rossetti et

al. (1998) demonstrated that patients with USN were able to adapt to the visual displacement. Furthermore, they showed that not only did the patients show improvements in their manual straight ahead pointing after PA training relative to before, but the after effect, following removal of the prisms, was almost twice that of healthy participants. Figure 2.1 shows an example of straight ahead pointing by patients and healthy participants before and after PA training. The figure shows that when asked to point straight ahead, before PA training, patients with USN point to the right of the midline in contrast to healthy control. The figure also shows that USN patients are more affected by the adaptation than healthy participants.

Figure 2.1: An example of straight ahead pointing by patients and healthy participants before and after PA training.



The Rossetti et al. (1998) study also showed that once the prismatic glasses were removed, all patients had improved on the classic neuropsychological tests of USN (line bisection etc). The authors noted that unlike other physiological (bottom-up) rehabilitation methods previously used to treat USN, the improvement seen during PA lasted for at least two hours after the removal of the prismatic glasses. The findings suggested that PA activated processes involved in brain plasticity related to multisensory integration and space representation.

In the Rossetti et al. (1998) study, participants were required to make visuo-manual responses. This system has long been known to be affected by PA. It is, therefore, of interest to look at whether PA can ameliorate symptoms of USN that do not involve visuomotor responses such as picture scanning, reading and so on.

2.2.3) The effects of PA on tasks that do not require visuo-manual responses

It would seem logical to suggest that the effects of PA should be restricted to visuo-motor tasks, because they share more common features with the visuo-manual adaptation procedure. However, research suggesting that PA can reduce USN in other sensory modalities and on non-manual tasks appears to demonstrate that the effects of PA on visuo-spatial defective abilities go beyond the visuo-manual parameters usually affected in normal subjects (Pisella, Rode, Farne et al. 2006).

Rode et al. (2001) asked two patients with left USN to complete three different tasks after PA training. On the first task, patients were required to point straight ahead, their heads being aligned with the body's sagittal axis. The second task was a free drawing task in which patients were asked to draw a daisy from memory. The final task was a mental imagery task in which patients were asked to mentally evoke a map of France and to name as many towns as possible on the map within two minutes. Prior to PA, both patients showed USN for mental imagery and reproduction from visual memory. On all tests, patients were tested before adaptation, immediately after adaptation and twenty-four hours after prism exposure. The findings for the mental imagery task, given immediately after PA, showed that patients named more towns on the 'mental' map than they did before PA training. Furthermore, the increase was mainly concerned with the generation of towns located on the left side of the map. This was significant because the level of space representation assessed by mental imagery tasks clearly differs from the sensory-motor level that is directly involved in the PA procedure. On the free drawing task, following adaptation, both patients showed improved drawing with reduced asymmetry of the daisy. On the pointing task, both patients showed improvement in straight ahead pointing. The findings also showed that when patients were tested twenty-four hours after prismatic adaptation, the amelioration of USN for mental imagery had

disappeared. The improvement seen on the daisy drawings, however, partly remained. Rode et al. (2001) suggest that this may be because the drawing task involved a manual response. The study is important as it suggests that the neural substrates underlying the imagery task and the drawing task differ in their level of space representation. The sensory-motor level (for the drawing task) may be directly affected by PA and thus produce longer lasting effects. However, the reduction of USN for mental imagery immediately after PA suggests that stimulation of the active processes involved in the plasticity of sensory-motor correspondences can also influence cognitive processes at the level of mental representations. The authors suggest that these results support the notion that the process of PA stimulates brain functions related to multisensory integration and higher order spatial representations. Rode et al. (2006) suggest that the mental imagery task is explicitly spatial in nature but that similar findings have been observed on a non-explicitly spatial mental task; the mental number line task.

The mental number task requires patients to bisect a mental number line. Zorzi et al. (2002) reported that the mental bisection between two numbers was systematically shifted to the right (towards the numerically larger number) in patients with USN. A study by Rossetti et al. (2004) showed that after PA training performance on the mental number line task was ameliorated in two patients with USN. Rode et al. (2006) suggest that PA influences the high level multimodal representations associated with spatial attention. They further argue that the effects of PA may stimulate processes involved in brain plasticity related to multisensory integration and space representation.

A study by Farne et al. (2001) compared visuomotor tasks (including line bisection, letter cancellation, bell cancellation) with visuo-verbal tasks (a visual-scanning test, which required a verbal description of the objects, an object naming task with thirty Snodgrass pictures intermingled with geometric shapes as distractors and word and non-word reading tasks). The two types of tasks exhibited a strictly parallel improvement after PA training. This improvement could still be observed twenty-four hours on all tasks after the prismatic glasses were removed. Similarly, Angeli et al. (2004) showed that PA significantly reduced neglect dyslexia. However, a subsequent study by Angeli

et al. (2004) showed that single word reading was not improved after PA training in patients with USN and hemianopia relative to USN patients without hemianopia.

A single case study by Humphreys, Watelet and Riddoch (2006) showed that patient MP showed beneficial effects of PA training on a visuo-spatial cancellation task but detection of errors on the contralesional side of words (word specific USN) and the detection of the contralesional side of chimeric faces (object based USN) remained unchanged after PA relative to the baseline condition. The authors argued that their patient showed object based USN which affected his performance on both the detection of errors in single words and the detection of gender difference for chimeric faces and that this object based USN was less affected by PA training than spatial USN (as assessed by cancellation tasks). This is consistent with other studies that have shown that chimeric face perception seem intractable by PA (Ferber, Dancert and Joanisse, 2003; Sari, Kalra, Greenwood et al. 2006).

2.2.4) The effect of PA in other sensory modalities

The research reviewed above suggests that PA training can ameliorate USN as measured by tasks that do not require a motor or manual component (mental imagery, visuo-verbal tasks). The next line of investigation was to determine whether PA training could ameliorate USN in other sensory modalities. A study by McIntosh et al. (2001) and Maravita et al. (2001) showed improvement in tactile USN after PA. Courtois-Jacquin et al. (2001) found an improvement in auditory USN as assessed by a dichotic listening task. These findings suggest that the effects of PA training are not restricted to the visual and motor systems.

2.2.5) The effects of PA on non-spatially lateralised deficits associated with (but not specific to) USN.

Bultitude, Rafal and List (2009) explored whether PA reduced the local processing bias associated with USN. Their study comprised of five patients with lesions to the right temporo-parietal cortex, because lesions to this area have been associated with USN and with hyperattention to local details of a scene and difficulty perceiving the global

structure. The patients were asked to identify the global or local levels of hierarchical figures before and after PA training. Prior to PA the patients had difficulty ignoring the local elements when identifying the global component. However, after PA this pattern was reversed, and patients showed greater global interference during local level identification. The authors concluded that PA improves non-spatially lateralized deficits that contribute to USN. They also suggest that the amelioration of the local processing bias after PA may be a result of a restoration of the activity bias between the left and the right hemisphere (see Kinsbourne 1970; 1993).

2.2.6) Are the plastic effects induced by PA training restricted to the acute phase of USN?

In his original study, Rossetti (1998) reported beneficial effects of PA training in a sample of left USN patients who were tested three weeks to fourteen months post-stroke. Jacquin et al. (1998) showed that a group of patients exposed to the adaptation procedure between five to twelve years post-stroke showed the same improvement as patients in Rossetti's (1998a) original study. Humphreys, Watelet and Riddoch (2006) showed that PA training ameliorated USN in a patient who had suffered with the disorder for 11 years. Several other studies have shown that PA training can ameliorate USN in patients 5-28 years post stroke (Rode, Pisella, Rossetti, 2003; Rode, Klos, Courtois-Jacquin et al. 2006). This demonstrates that the plastic effects induced by PA are not restricted to the acute phase of USN.

2.2.7) How long do the effects of PA training last?

After one five-minute session of PA training, Rossetti et al. (1998) reported USN amelioration two hours later. Farne et al. (2002) reported beneficial effects twenty-four hours after a single PA training session. Pisella et al. (2002) reported beneficial effects four days after a single PA training session. However, Farne (2001) reported no beneficial effects one week after a single PA training session while Rossetti and Rodes (2004) reported that a single session of PA training did not produce long and lasting effects. Rossetti and Rodes were of the opinion that in order to produce sustained gains, PA training must be repeated over a number of sessions. Frassinetti et al. (2002) trained

patients twice daily over a period of two weeks. Their research showed that PA training gains could be maintained five weeks post-training. Serino (2005) gave their patients ten sessions of PA over a two-week period. They showed that PA training gains could be maintained up to three months post-training. A single case study by Humphreys, Watelet and Riddoch (2006) demonstrated that the beneficial effects on PA on visuo-spatial tasks were maintained up to one year post PA training. McIntosh (2002) suggested that it is possible some patients show improvement for a longer time than others; the reason for this at present is unclear.

2.2.8) Does improved performance after PA training generalise to functional tasks?

It is clear that after PA training USN symptoms, as measured by standardised neuropsychological tests, can be significantly ameliorated. However, other rehabilitation techniques used to treat patients with USN have been criticised for being task specific. For example, patients with USN are often trained to overtly scan the left side of space. Rossetti et al. (2004) point out that these 'rehabilitated' patients often perform perfectly on classic tests of USN and then walk into the door when leaving the room! It is therefore important to explore whether the effects of PA training are task specific or whether they generalise to everyday tasks.

Research has shown that PA can improve various aspects of USN, including postural imbalance (Tilikiete et al., 2001) and wheelchair navigation (Rosetti et al., 1999) in addition to those measured by standardised neuropsychological tests. Keane et al. (2006) carried out an observational study to explore the functional effects of PA training on patients with USN after a stroke. Four patients with USN (all sixty days post-stroke) were given five ten-minute PA training sessions over a period of twelve to seventeen days. Prior to training, patients were given three subtests from the Behavioural Inattention Test (BIT) including the line bisection, line crossing and letter cancellation tasks. Their straight ahead pointing was assessed and the patients were given several functional tasks including the FIM instrument, the Catherine Bergego Scale (CBS), and an object avoidance test which assessed their ability to avoid colliding with objects whilst walking. All patients improved significantly after PA training on the BIT subtests

and straight ahead pointing, exhibited functional improvements on the FIM instrument and the Catherine Bergego Scale and two of the patients showed improvements in obstacle avoidance (whilst walking). This study suggests that the effects of PA training do generalise to functional tasks. However, the study had a small sample size and did not include a control group.

2.2.9) Theories of the mechanisms underlying the effects of PA training on the amelioration of USN

It is not yet clear what mechanisms underlie the amelioration of USN after PA training; however, several theories have been put forward. A number of the most important of these theories will now be considered. First the reference shift hypothesis will be considered.

2.2.9.1) The reference shift hypothesis

One of the manifestations of the USN syndrome is an alteration of the egocentric reference frame. For example, Jeannerod et al. (1987) and Werner et al. (1953) showed that when their patients with USN were asked to point straight ahead in the dark, their subjective straight ahead pointing deviated to the right of their midline. These research findings have led to the 'reference-shift' hypothesis of USN. The hypothesis states that this orientation bias is due to an 'illusory' rotation of the egocentric reference frame. The hypothesis suggests that this orientation bias, in which patients seem to be mentally rotated ipsilesionally relative to the midline, constitutes the core of the USN syndrome. This hypothesis, therefore, allows for the possibility that treating this orientational bias should improve general USN symptoms and not merely those relating to orientation.

Support for the 'reference shift hypothesis' comes from the temporary improvement of USN after specific physiological interventions, which serve to compensate for the apparent shift in the egocentric reference (Pizzamiglio et al., 1990; Rode et al., 1999; Rode et al., 1994). However, this hypothesis has been challenged by Chokron and Bartolomeo (1997), Farne, Ponti and Ladavas, (1998) and by Bartolomeo and Chokron (1999) all of whom reported that not all the USN patients in their studies exhibited a

rightward shift of the egocentric reference. Of the 43 patients tested in these three studies, only 27 were reported to show a rightward deviation in straight-ahead pointing. Farne et al. (1998) further showed that the same proportion of patients with right hemispheric damage but no USN showed these orientational biases as right hemisphere damaged patients with USN. However, this does not mean that PA training does not work by shifting the egocentric reference frame because PA training is not effective for all patients. It is therefore possible that it may work only for the patients who exhibited a rightward shift of the egocentric reference in the first place.

Pisella et al. (2002) carried out two single case studies (patients S.A. and P.E.). Both patients had USN and were assessed for a period of five days; they were tested one day before and four days after PA training. The patients' performance was repeatedly measured on straight ahead pointing tasks and line bisection tasks. The first aim of the study was to investigate the duration of beneficial effects after PA and the second aim was to determine whether these beneficial effects were the same for all patients and whether these effects could be seen on both tests.

Pisella et al (2002) aimed to determine how long the beneficial effects induced by PA would last for and whether the improvement seen on line bisection and pointing tasks would correlate. They argued that if there is actually a 'deviation of the internally represented mid-sagittal plane of the body, a co-variation would be expected between the two types of test performance.' They further suggest that if the deviation of the egocentric reference and USN symptoms rely on separate mechanisms, it may be possible to alter one of them without affecting the other. Thus, if no correlation is observed between performance on the two tests (straight ahead pointing task and line bisection task), then the mechanisms underlying line bisection performance and this 'reference shift' must be independent of each other and would each be responsible for a particular USN symptom. The authors, therefore, suggest that if line bisection and straight ahead pointing were to show the same evolution over time after PA, this would be consistent with the hypothesis that the PA effect on cognitive systems is mediated by an alteration in the egocentric reference. The findings showed that during the late phase

following PA (days two to four post-training), the effects of the two symptoms investigated were doubly-dissociated between patients S.A. and P.E. Immediately after PA, patient S.E. showed no bias on the line bisection task or the straight ahead pointing task. Four hours later, S.E. maintained his PA training gains on the line bisection task whereas the rightward shift of the egocentric reference frame reappeared and was comparable with pre-tests. Patient P.E. improved on the straight ahead pointing task after PA training and maintained this improvement four hours later. However, the line bisection was not affected by the PA procedure. Pisella et al. (2002) argue these results indicate that the beneficial effects of PA on spatial cognition are not mediated by a modification of the egocentric reference frame and that these two symptoms probably depend on distinct mechanisms in different, though neighbouring, brain areas.

2.2.9.2) Does synergy between short term plasticity mechanisms involved in adaptation and the long term plasticity mechanisms induce recovery from USN after PA training?

Luaute et al. (2000) suggested that one explanation for the effects of adaptation on patients' performance could be the existence of 'cross-talk or synergy between short term plasticity mechanisms involved in adaptation and the long term plasticity mechanisms involved in recovery.' To investigate this hypothesis, Luaute et al. (2000) compared the effects of left versus right deviating prisms with patients with left USN. The rationale behind this is that left and right deviating prisms produce symmetrical visuomotor after-effects in healthy participants; however, leftward deviating prisms did not improve USN in five patients (Rossetti et al., 1998) with left USN. This result is surprising as one would expect, because of the symmetrical effects in healthy participants, that PA training should generate the same amount of plasticity and thus affect right and left spatial USN in the same way. This finding, therefore, excludes the possibility that the effects of adaptation are due to the synergy between short term plasticity mechanisms involved in adaptation and long term plasticity mechanisms involved in recovery. It also demonstrates that the effects of PA are not due to general cortical arousal; if this were the case improvements would be expected for both right and left USN patients.

2.2.9.3) Does PA training induce recovery of USN by means of an adaptive redistribution of spatial attention?

Pisella (1999) demonstrated that the pathological left/right attentional gradient observed in USN patients could be reduced following PA. Another mechanism that may mediate USN amelioration after PA training, therefore, is a shift in attention. Berberovic et al. (2004) assessed straight ahead pointing without vision and performance on a temporal order task in four patients with left USN. Before and after PA training patients were asked to judge the temporal order of stimuli presented successively in opposite visual fields. Before PA training, patients showed a slight rightward deviation in straight ahead pointing. After PA training, patients showed a leftward deviation (after-effect) on the straight ahead pointing task. On the temporal order task, patients showed the characteristic ipsilesional bias. In order for the left stimulus to be judged as appearing first, it had to precede the right stimulus by 427 milliseconds. However, after PA training the left stimulus only had to appear 98 milliseconds before the right for it to be judged as appearing first. Berberovic et al. (2004) argue that these findings suggest that PA ameliorated the ipsilesional attentional bias by rebalancing the distribution of spatial attention towards the left-side.

It has been established that directing attention away from a particular aspect or location of a visual scene can alter one's perception of that location or aspect. Harvey et al. (2000) showed that when attention is cued towards one side of a line during a line bisection task, participants experience a shift in the subjective midpoint towards the cued side. The authors therefore suggest that the presence of an attentional bias following PA could explain the ameliorating effect of PA.

A study by Morris et al. (2004) employed a visual search task to assess whether the known adaptive visuomotor components of PA are accompanied by an adaptive redistribution of spatial attention in healthy participants (Experiment One) and in right hemisphere damaged patients (Experiment Two). Experiment one used a visual search paradigm to investigate whether visuomotor adaptation to left or right displacing prisms could induce an attentional bias in healthy participants. In this experiment, participants

were given a 'simple' search task (requiring little or no spatial attention) and a 'complex' search task which has been shown to be strongly dependent on selective attention mechanisms. Reaction times to detect targets on simple search paradigms are relatively unaffected by the number of distractors in the search array. The reason for this is thought to be that 'simple' search tasks reflect the operation of 'pre-attentive' mechanisms. Therefore, performance on such tasks should be unaffected by a change in the spatial distribution of attention following PA. In contrast, reaction times for complex search paradigms increases as the number of distractors increases. This is because selective attention is thought to be allocated serially to each item in the array until the target item is detected (Wolfe, 1998). In the study, participants were given a simple and a complex search task before and after adaptation to right and left deviating prisms. Since visual search tasks are sensitive to even mild lateral impairments of spatial attention, visual search tasks should be sensitive to any change in the distribution of attention. Morris et al. (2004) suggested that if PA did induce a redistribution of selective attention then a leftward displacement of the visual field would induce a rightward bias in performance on the complex search task but not on the simple search task. One would expect, therefore, to see longer reaction times and more errors for targets located towards the left side of the array accompanied by faster reaction times and fewer errors for right-sided targets on complex search trials. Following PA there was, however, no change in performance for either task as a function of target location. Morris et al. (2004) suggest that although alignment between perceptual and motor space is altered during PA, this is not accompanied by a redistribution of spatial attention in healthy volunteers. These findings do not support the view that there is a spatial redistribution of spatial attention. Morris et al. (2004) suggest that PA distorts representations of spatial extent but this effect is not mediated by an attentional bias. As the after-effects of PA in healthy participants have been shown to be very subtle (Michel et al., 2003), it is possible that if there were a redistribution of attention it is too subtle to measure reliably. However, because the adaptation procedure has been shown to ameliorate symptoms of USN, a disorder characterised by a pathological gradient of spatial attention, one would expect to see more pronounced changes in visual search behaviour after PA training if in fact spatial attention were redistributed.

In Experiment two, Morris et al. (2004) explored the redistribution of attention hypothesis. The experiment was identical to Experiment one. However, a group of right hemisphere USN patients were tested as opposed to the group of healthy controls tested in Experiment one. The rationale was that if improvement in USN after PA was due to an amelioration of the pathological spatial attention gradient, then these patients would show an improved performance on visual search tasks following adaptation; this improvement would be especially evident in the complex task. The findings provided no support for the hypothesis that PA improves symptoms of USN by ameliorating the gradient of spatial attention towards the ipsilesional side of space. Morris et al. (2004) point out that selective attention is critical for visual search tasks because they require a speeded response, in contrast to other methods commonly employed after PA training where no speeded response is required. The authors suggest that the commonplace non-speeded tasks are insensitive to the temporal dynamics of spatial perception. They suggest that some other component of the USN disorder may mediate the improvement after adaptation, despite an unchanged gradient in spatial attention towards the ipsilesional side of space. The study is important in that it suggests that improvement is not mediated by a redistribution of spatial attention and that using speeded tests (those requiring fast recorded responses) may be a more sensitive way of revealing the presence of a residual spatial gradient that remains unchanged by the PA technique than a non-speeded response task. Morris et al. (2004) argued that speeded search tasks are a better measure of visuospatial attention than non-time restricted tests, since patients can use other strategies to complete the non-time restricted tasks and these tasks are insensitive to the temporal dynamics of spatial perception.

Saevarsson, Kristjansson, Hildebrandt and Halsband (2009) challenged the claims of Morris et al. (2004) that PA only ameliorates target detection on non-speeded tasks of USN. They suggest that Morris et al. (2004) may not have found an effect of PA on a visual search task because patients received visual feedback as to whether their key press responses were correct or incorrect. Saevarsson et al. (2009) argue that feedback may disrupt positive after effects of PA in patients with USN (Lee and Lee, 2006; Redding,

Radar and Lucas, 1992; Redding, Rossetti and Wallace, 2005). Saevarsson et al. (2009) suggested that feedback in visual search may lead to de-adaptation effects for patients with USN because feedback may result in strategic thinking and may thus increase cognitive load for the patients. The authors argue that this explanation ties in with findings reported on healthy non-brain damaged participants suggesting that increased cognitive load (Redding et al, 1992) and strategic thinking (Lee and Lee, 2006) can lead to de-adaption. Moreover, Hussain et al. (2001) argued that patients with USN suffer from impairments in spatial working memory which may explain why increased cognitive load eliminated the effect of PA in the study of Morris et al. (2004) and Saevarsson et al. (2009). It should also be noted that Kerkoff (1998) showed that feedback based visual learning improved visual search in USN (Kerkhoff, 1998) however, in this experiment feedback was given over many sessions.

To address the issue of feedback Saevarsson et al. (2009) carried out an experiment to assess any beneficial effects of PA on a single feature 'pop out' visual search task in two groups of patients with USN: one group was given a speeded version of the task with feedback (same conditions as Morris et al. 2004) and the other group was given a non-speeded version with no feedback. All patients were also given six pen and paper tests of USN before and after training (Albert's test, line bi-section, line cancellation, number cancellation, copy drawing and free hand drawing). Four patients with USN who were given the speeded visual search and feedback (auditory and verbal) showed no effect of PA on the pen and paper USN tasks and the time taken to complete these tasks was comparable before and after PA. Left and right-sided target detection and the identification of target absent trials did not differ significantly after PA from the baseline condition. However, detection of right-sided and left-sided targets became significantly faster whereas detection of target absent trials became slower. The four patients with USN given the non-speeded visual search without feedback showed a significantly greater average number of correct responses on the six pen and paper task of USN after PA compared with before; patients also completed the tasks more quickly after PA training. On the non-speeded visual search task (with no feedback) patients detected more left-sided and right-sided targets after PA than in the baseline condition. Right-

sided, left-sided and target absent trials were identified more quickly after PA training than in the baseline condition. The authors concluded that PA can improve visual search in patients with USN and that these beneficial effects can disappear with feedback.

Although Saevarsson et al. (2009) argue that the presence of feedback was the critical variable in determining whether PA was effective or not, the design of the study does not eliminate the possibility proposed by Morris et al. (2004) that speed was the critical variable in determining whether PA was effective. The design compared speeded-response and feedback with non-speeded response and no feedback. It may have been more useful to have included two more conditions, 'non-speeded response and feedback' and 'speeded response and no feedback', in order to tease apart the relative contribution of speeded versus non-speeded tasks and feedback versus no feedback.

2.2.9.4) Does PA training induce recovery of USN by inducing a leftward ocular deviation that facilitates the exploration of previously neglected space?

As well as modifying visuomotor representations, PA may also induce a leftward ocular deviation and this deviation in eye movements may facilitate the exploration of previously neglected space (Ferber, 2003; Angeli, Benassi and Ladavas, 2004). However, Ferber (2003) showed that despite such a change there was no corresponding improvement in judgements of the relative salience of ipsilesional compared to contralesional information. She presented two chimeric faces to a patient with left USN. Each face had a happy side and a neutral side. The patient was asked to judge which of the two faces had a happier expression overall. Prior to PA, the patient restricted his eye movements to the ipsilesional side of the faces and selected the happier face as the face that was smiling on the right side of space. Following adaptation, the patient's eye movements were not restricted to the ipsilesional side of space, in fact the patient made more contralesional saccades than ipsilesional saccades. However, the patient showed no change in his ipsilesional bias on the task. These findings suggest that PA training may improve space exploration towards the contralesional side of space but that this contralesional information may still be neglected, or at least remain less salient than ipsilesional information (Morris et al, 2004). However, Maravita (2003) showed that

after PA training his patients did become aware of visual and tactile stimuli presented in the neglected field. Ferber (2003) suggests that these conflicting findings can be explained by the different location of the lesions between the two patients.

Ferber (2003) argues that PA training did not improve her patient's performance on the emotional chimeric face test because the patient's USN was not related to the type of exploration deficit associated with parietal lesions, which PA successfully treats. The patient had a superior temporal gyrus (STG) lesion. Ferber (2003) argues that spatial awareness is mediated by the STG rather than the parietal lobe and so patients with lesions to this region may remain unaware of contralesional events despite being able to make saccadic movements towards them. Evidence from monkey studies supports this argument. Watson et al. (1994) showed that damage to the STG caused unawareness for contralesional events whereas damage to the inferior parietal lobules did not. Karnath, Ferber and Himmelbach (2001) controversially made the same argument based on human data (details can be found in Chapter One). Watson et al. (1994) argue that the dorsal (where) and the ventral (what) streams converge in the posterior superior temporal lobe and consequently awareness of events in space is dependent on this convergence. However, Colby and Goldberg (2003) suggest that the parietal lobes mediate spatial awareness.

Another explanation for the conflicting findings of Ferbers (2003) and Maravita (2003) is that the tasks used to assess awareness are clearly very different. Maravita et al. (2003) asked the patient to report the presence of a stimulus whereas Ferber (2003) asked her patient about the emotionality of faces that express two emotions. Beversdorf and Heilman (2003) suggest that after PA patients may indeed gain some degree of multimodal awareness of contralesional stimuli, but the degree of improvement is not sufficient to allow complex perceptions. Redding and Wallace (2006) point out that the patient in Ferber's study showed an extreme bias in straight ahead pointing before PA and although the patient's after-effect was extremely large, it may not have been large enough to shift subjective straight ahead pointing into the contralesional side of space.

A difficulty for the eye movement account of recovery from USN is that as well as having purely visual effects PA can improve contralesional tactile perception in USN (Maravita et al, 2003). Maravita et al. (2003) suggest that their patients' improvements cannot be entirely explained by an alteration of visual exploration because faulty exploration plays no apparent role in tactile extinction. They go on to suggest that PA training may have improved visual and tactile USN symptoms by influencing the high level multimodal representations associated with spatial attention. Gainotti (1993) suggests that much evidence exists indicating that eye movements may orient attention towards the appropriate part of space not only during visual tasks but also in the tactile or auditory modality. Furthermore, crossmodal attention studies have demonstrated a strong interaction between vision and touch in modulating spatial attention (Driver and Spence, 1998; 2004).

Angeli et al. (2004) investigated whether PA induces eye deviation to the left thereby facilitating the exploration of the neglected side of space. In their experiment, patients with USN were asked to fixate a central cross displayed on a computer screen. Immediately after the cross had disappeared, a letter string was presented. Patients were asked to read aloud the letter string as fast as possible. Eye movements were recorded during the task. Patients were given the task before and after PA training. In order to verify whether the eye movement improvement was due to a simple bias induced by PA in the direction of gaze, patients with and without neglect dyslexia were studied. Seven patients had neglect dyslexia and hemianopia and seven patients had USN with no hemianopia. After PA training, the patients with USN and hemianopia did not improve on the reading task in contrast to patients who had USN but no hemianopia who improved significantly. The latter showed an increase in left-sided eye movements relative to patients with USN and hemianopia who showed no improvement in left-sided eye movements. Angeli et al. (2004) argue that the oculomotor improvements found for the USN patients without hemianopia are not due to a simple error induced by PA training but can be better explained by a complex interaction between sensory stimulation and oculomotor deviation. They suggest that in USN patients without hemianopia, visual signal registration, although partial, may provide a signal to move

the eye (and visual attention) towards the left-sided letters and, as a consequence of this eye movement, detection of the left-sided information improved. However, in USN patients with hemianopia, the absence of visual stimulation means that a signal to move the eyes (and thus visual attention) in a leftward direction is not provided and as a consequence neglect dyslexia was not ameliorated. These authors, therefore, suggest that amelioration of USN causes the improvement in eye movements rather than eye movement improvement causing amelioration of USN.

Serino et al. (2007) also suggest that the improvement in USN following PA may occur as a result of what they refer to as 'oculomotor resetting'. They argue that a leftward deviation of the eye is prompted by the incremental leftward deviations of the arm that occur during prism exposure. They argue that when patients point to the right of a target on the first trial of prism exposure (whilst wearing glasses that shift the visual field to the right) patients must correct their reaches further and further leftwards until accuracy is achieved. They suggested that because eye and hand are yoked during goal-directed reaching (e.g. Carey, Coleman, and Della Sala, 1997; Fisk and Goodale, 1985; Jackson, Newport, Mort, and Husain, 2005), the eye also deviates leftwards and this ameliorates scanning behaviour and prompts leftward orientation.

2.2.9.5) Does PA training ameliorate USN by enabling relearning of visual-motor strategies?

Redding and Wallace (2006) have attempted to explain the means by which PA training ameliorates USN. In order to understand the basis of their theory, some key concepts and terminology pertaining to PA theory and relevant aspects of motor control first must be explained. In order to carry out a perceptual-motor goal directed task, such as reaching for a pen, a number of events must occur. Reaching for a pen is a routine perceptual-motor task, so a previously learned coordinate structure must be retrieved. This coordinate structure links sensory-motor systems from eye to hand. If the task was to walk to one's front door, a different coordination of sensory-motor systems would be retrieved. Redding and Wallace (2006) argue that the generalised movement plan includes input-output details at subordinate levels in order to achieve a task specific

movement plan. With respect to the visual-motor aspect (input), Redding and Wallace (2006) suggest that a regional task work space is identified to include the goal object among surrounding objects that may influence the execution of the motor plan (surrounding obstacles). It is important to note that the regional task workspace is a selected area of space; it can be considered analogous to the attentional spotlight that enhances awareness of what falls in its beam. The contents of the regional task workspace are considered before a specific movement plan is elicited. Redding and Wallace (2006) refer to the strategic positioning of the regional task workspace as 'calibration'. Redding (2007) argued that calibration simply means the attentional focus on a limited region of space that is involved in a given task. Once the task workspace has been selected, this visually prescribed movement plan is sent as a feed-forward movement command structure to the limb. This feed-forward movement plan is thought to involve a predicted set of movements such that deviations can be anticipated and corrected before they can occur or before they become too large. With respect to the output proprioceptive-motor aspect, the processes that control the limb in question interpret the feed-forward commands and calibrate a limb task work- space accordingly. If the starting point of the limb is visible, its position is specified in a visually derived command structure. However, if the starting point of the limb is not visible, limb control is specified in a proprioceptive command structure. If the limb becomes visible during the movement plan, visual feedback can be implemented to send corrective commands coded in terms of relative distance and direction to the goal object. Highly practised tasks can be largely automatic whereas novel tasks need to be learned slowly. Once a regional task workspace has been identified, conscious awareness is largely restricted to the contents of the task workspace.

Coordinate systems have different reference frames. For example, spatial positions for the visual-motor system are coded along coordinate axes centred on the head, whereas spatial positions for the proprioceptive-motor system are coded along coordinate axes centred on the shoulder. The visual reference frame is mostly orientated frontally whereas the proprioceptive-motor system is mostly orientated laterally (with respect to the body). Thus, different coordinate systems have different origins and orientations. It

is therefore necessary that movement plans formulated in one sensory-motor coordinate system are transformed for use by different sensory-motor systems. The process of adjusting or transforming these constant differences in spatial coordinates between sensory-motor systems is called alignment. Misalignment occurs when the constants change. Realignment is then necessary to re-establish corresponding spatial mapping among sensory-motor systems.

PA is a unique way to study misalignment and realignment as it introduces misalignment into an aligned system.

Redding and Wallace (2006) propose that USN reflects a dysfunction in selecting the appropriate region of space for a given task. They argue that while healthy participants can strategically size and position (calibrate) their task workspace around task relevant objects, USN patients have a deficit in both strategic abilities; the task workspace is pathologically reduced in size and patients cannot strategically shift its position. In their view, USN arises, in part, from dysfunctional perceptual-motor processes that strategically position and adjust the size of the regional task workspace. That is, patients with USN have a calibration deficit. Redding and Wallace (2006) argue that spatial realignment with rightward prismatic displacement substitutes for this dysfunctional calibration, forcing a leftward shift of the (pathologically narrowed) task workspace so that more of the neglected left space is included. This repositioning of the task workspace enables relearning of visual-motor strategies. These re-learned strategies have lasting effects that persist long after alignment returns to 'normal'.

Redding and Wallace (2006) argue that, after PA training, patients are able to strategically position the task workspace but are unable to size the task workspace. They claim that PA shifts the egocentric coordinates of a sensory-motor reference frame that brings at least part of the neglected hemispace into the dysfunctional task workspace. Thus PA training substitutes for the dysfunctional positioning of the task workspace but it does not substitute for the dysfunctional sizing of the task workspace. Redding and Wallace (2006) further argue that amelioration of the dysfunctional positioning enables

re-learning of strategic processes (calibration) and that this may partially restore the ability to size the workspace. They suggest that their account is most consistent with attentional theories of USN (Kinsbourne, 1993). They argue that calibration is an attention-like process that, when dysfunctional, produces a biased task workspace selection which increases the salience of the right hemispace but does not preclude influence from the left hemispace (Redding and Wallace, 2006).

2.2.9.6) Does PA training ameliorate the remapping deficit in USN?

Pisella and Mattingley (2004) suggest that a remapping deficit in the parietal cortex could account for lack of awareness of space in USN (details of this theory can be found in Chapter one, section 1.6.4). They argue that the remapping deficit does not itself explain all the symptoms of USN but should be considered in addition to an orientation bias and a bias for local detail. They speculate that PA training may ameliorate the remapping deficit in patients with USN such that objects/events on the contralesional side of space (coded in salience maps) are no longer 'overwritten' and thus precluded from conscious awareness. This theory has yet to be empirically verified. However, Pisella and Mattingley (2004) suggest that the remapping mechanism is damaged after lesions to the posterior parietal cortex (PPC), including the intraparietal sulcus (IPS). A PET imaging study by Clower et al. (1996) showed that the only area activated during PA was the posterior parietal cortex contralesional to the adapting limb, specifically area PEG on the lateral bank of the intraparietal sulcus.

2.2.9.6) Anatomico-functional hypothesis of the effects of PA training

Pisella, Rode, Farne et al. (2006) propose that the beneficial effects of PA training may be the consequence of changes in relative hemispheric activation. This relates to Kinsbourne's (1970, 1993) assertion that restoring the balance between the right and left hemisphere would ameliorate symptoms of USN. As previously discussed, Kinsbourne argued that the left and the right hemispheres direct attention contralaterally in a mutually opponent manner. After damage to the right hemisphere, function in the left hemisphere becomes disinhibited. Consequently, USN is considered to be a hyperattention to the right visual field rather than an impairment in leftward attention.

Pisella, Rode and Farne et al. (2006) proposed a two stage model to explain the clinical effects of PA based on studies of visuo-motor adaptation in patients with cerebellar lesions (Pisella et al. 2005) and bilateral lesions to the parietal lobe (Pisella et al., 2004). They argue that the beneficial effects of PA rely on a network of brain areas where the visual error-signal generated by rightward deviating prisms is initially processed in the left occipital lobe. The information is then transferred to the right cerebellum where visuo-motor realignment takes place. Pisella et al. postulate that the effects of PA may be mediated through the modulation of cerebral areas in the left hemisphere via bottom-up signals generated by the cerebellum. They suggest that left hemisphere areas may include the temporal, frontal and posterior parietal cortex, the dentate nucleus and subcortical structures. Pisella et al. (2006) argue that the beneficial effects of PA might therefore be mediated by the recruitment of pathways in the left hemisphere that are 'functionally homologous to those involved in spatial cognition in the damaged right hemisphere'. With respect to the argument that PA stimulates areas in the left hemisphere to take on functions that would ordinarily be served by the damaged right hemisphere, Bultitude et al. (2009) (argue that this model could just as easily provide for a reduction in left hemisphere activity after PA, thus reducing the inhibition of residual right hemisphere functioning. Luaute et al. (2006b) found reduced activity in the left posterior parietal cortex in patients with USN who had had PA training; this correlated with improved performance on standard tests of USN.

2.2.10) Summary

PA has been shown to be a promising technique in rehabilitating USN. As well as ameliorating the performance of patients with USN on tests that require visuo-motor responses such as cancellation tests, line bisection and so on (Rossetti et al., 1998) PA has also been shown to ameliorate USN for mental imagery (Rode et al., 2001; Rossetti et al., 2004), neglect dyslexia (Angeli et al. 2004 - although see Humphreys, Watelet and Riddoch, 2006), auditory USN (Courtois-Jacquin et al., 2001), tactile USN (Maravita et al., 2001), wheel chair navigation (Rosetti et al., 1999) and postural imbalance in patients with USN (Tilikiete et al., 2001). PA has also been shown to ameliorate the

local processing bias which is not part of the USN syndrome but often co-occurs with USN, exacerbating the symptoms (Bultitude, Rafal and List, 2009)

Unlike some of the other techniques for rehabilitating USN, such as attentional scanning (Pizzamiglio et al., 1992; Ladavas et al., 1994), the administration of PA is not labour intensive and does not require patients to become explicitly aware of the contralesional side of space. In addition PA is cost effective and relatively straightforward to administer. Moreover, the effects of PA have been shown to be long lasting (Frassinetti et al., 2002; Serino, 2005; Humphreys, Watelet and Riddoch, 2006). The exact mechanisms that underlie the amelioration of USN symptoms after PA training are not clear, however, several explanations put forward have been discussed in this review. What is clear is that PA is a promising technique in rehabilitating a disorder which has been shown to be one of the best single predictors of poor functional outcome after a stroke (Denes et al., 1982; Kinsella and Ford, 1985).

Chapter 3: General aims and methods of investigation

Section 3.1 and 3.2 of this Chapter details the two main experimental questions being investigated in this thesis and the reasons for asking them. Sections 3.3 to 3.6 outline the general methodology used, the participants and the statistical treatment of the data obtained.

3.1) Is amelioration of the ipsilesional detection bias in USN patients after PA accompanied by modification of the ipsilesional RT bias?

When working with patients who exhibit left USN, two behavioural characteristics immediately become apparent. First, the patient begins scanning space on the ipsilesional side and gradually moves their search in a contralesional direction. This ipsilesional scanning behaviour, characteristic of USN, but not of healthy controls, is thought to be the result of a pathological gradient of attention (Behrmann et al., 1997). This can be captured behaviourally by recording patients' RTs to targets presented across the X axis of a computer screen. Patients with USN show an RT gradient whereby the further the target deviates from the right, the greater the time taken to respond to the target (Smania, Martini, Gambina et al., 1998). This thesis will use the term '**ipsilesional RT bias**' to refer to this behavioural characteristic of USN. The second behavioural characteristic that becomes apparent when working with someone with left USN is that the patient is more likely to neglect or ignore an object the further to the left it appears in the visual field. This thesis will use the term '**ipsilesional detection bias**' to refer to this characteristic.

3.1.1) Rationale for experiments to be reported

It has been proposed that PA increases target detection in patients with left USN by facilitating a redistribution of their spatial attention. Rode, (2003). came to this conclusion after showing that PA significantly improved contralesional target detection in their USN patients (i.e. the ipsilesional detection bias was reduced after PA). Since these authors say nothing about patients' response times, they presumably believe that the detection bias and the RT are caused by a single functional impairment and that there

is a direct relationship between the ipsilesional detection bias and the ipsilesional RT bias.

In contrast to this view, Pisella and Mattingley (2004) infer that the ipsilesional RT bias and the ipsilesional detection bias are caused by separate deficits and may dissociate. The ipsilesional RT bias observed in patients with USN is thought to occur after damage to the salience map, the first level of visual representation (Pisella and Mattingley, 2004). A deficit here creates a gradient of impairment, with a greater proportion of neurones ready to respond to ipsilesional locations. This is reflected behaviourally in patients with left USN by an ipsilesional RT bias (Smania, Martini, Gambina et al., 1998). Pisella and Mattingley (2004) suggest that a second deficit underlying the manifestation of USN is a remapping deficit which occurs between the first level of visual representation (the salience map) and the second level of visual representation (the winner takes all array). They argue that a remapping deficit can explain unawareness for the contralesional side of space, that is, the ipsilesional detection bias.

It has been argued (Pisella and Mattingley, 2004)) that patients with extinction may have a deficit at the level of the salience map and thus show an ipsilesional RT gradient but, unlike patients with USN, do not have an additional impairment which creates a consistent lack of awareness of left-sided objects (that are presented for an unlimited period of time). Pisella and Mattingley (2004) suggest that extinction patients only show a lack of consciousness for left-sided targets in the non-ecologically valid situation of simultaneous very brief target presentation. Thus patients with extinction and USN both have a primary deficit at the level of the salience map which results in an ipsilesional gradient of attention. However, USN differs from extinction in that USN patients have a secondary deficit (which disturbs remapping) that creates a consistent lack of awareness of contralesional targets even when targets are presented in unlimited time.

To summarise, previous studies have shown that patients with left USN detect more contralesional targets after PA relative to before PA (i.e. the ipsilesional detection bias is reduced after PA). Several authors have argued that this may be due to PA facilitating a

redistribution of spatial attention (Rode, 2003, Pisella, 1999). However, it is the ipsilesional RT bias that is the behavioural correlate of the ipsilesional attentional bias characteristic of USN and not the ipsilesional detection bias. No research currently exists demonstrating that the ipsilesional RT gradient and the ipsilesional detection gradient are in fact related to one another. Thus, it is not clear whether improvement in contralesional target detection is accompanied by amelioration of the ipsilesional RT bias after PA training. The view that two separate deficits underlie the manifestation of USN implies that the ipsilesional RT bias and the ipsilesional detection bias may dissociate (Pisella and Mattingley, 2004) and that PA may ameliorate the ipsilesional detection bias but not the ipsilesional RT bias. One aim of this thesis is to offer some insight into the relationship between the RT and detection bias and the relationship between PA training and the ipsilesional RT and detection biases.

Pisella and Mattingley (2004) suggest that PA training may ameliorate USN by either a) ameliorating the ipsilesional attentional bias or b) by improving the remapping deficit. Two scenarios follow from this view:-

A) If PA ameliorates the ipsilesional attentional bias by facilitating a redistribution of spatial attention (Rodes, 2003), the ipsilesional RT gradient characteristic of USN should be 'normalised' after PA and this change in the RT function will be accompanied by increased detection and awareness of contralesional targets if the RT and detection bias are related.

B) If PA training works by ameliorating the remapping deficit then the ipsilesional RT bias will remain unchanged whereas detection of contralesional targets will be improved.

Observing the effects of PA on the ipsilesional detection bias and the ipsilesional RT bias is not the only way to explore whether these two components of the USN syndrome are intrinsically related. The dissociation between near and far space in patients with USN has been reported many times in the literature (Marshall and Halligan, 1991;

Cowey, Small and Ellis, 1994; Pitzalis et al. 2001). Specifically it has been shown that patients may neglect contralesional targets in near but not in far space or vice versa; this suggests that the ipsilesional detection bias may dissociate depending on a target's position on the Z axis. However, no one has explored whether this is also true of the ipsilesional RT bias. If the detection bias and the RT bias characteristic of USN are related one would expect that if a patients' detection in near/far space is significantly better than in far/near space then the attentional gradient would be steeper in the section of space in which the patient shows the most impaired detection. This question will be addressed in a single case study of a patient whose detection in near space is significantly impaired relative to her detection of the same targets in far space.

Impaired visual search is a common symptom in USN (e.g. Behrmann, Ebert, and Black, 2004; Husain et al., 2001). Visual search tasks are useful tests for USN since they mimic in many ways the attentional requirements of many daily circumstances. Typically, patients miss a great number of the targets that are presented on the left side of a search array (e.g. Husain et al., 2001; Kristjánsson, Vuilleumier, Malhotra, Husain, and Driver, 2005; Saevarsson, Jóelsdóttir, Hjaltason, and Kristjánsson, 2008). Visual search tasks have been shown to be reliable measures of USN as well as being sensitive to the distribution of spatial attention (Riddoch and Humphreys, 1987; Wolfe, 1998; Olk et al., 2002). In addition, visual search tasks allow one to measure both detection and RT performance, unlike the pen and paper tasks that have conventionally been used to evaluate the effects of PA which measure only the patient's ability to detect targets. Consequently, a visual search task was used in the experiments reported in this thesis to investigate whether amelioration of the ipsilesional detection bias is accompanied by modification of the ipsilesional RT bias after PA training relative to before training.

3.2) Does PA training ameliorate USN in both near and far space? Does the mode of training (near or far) differentially affect performance in near and far space?

To recapitulate, near space, also referred to as peripersonal or reaching space, is the space within arm's reach whereas far space, often referred to as extrapersonal space, is the section of space beyond arm's reach, the space in which objects cannot be reached.

3.2.1) Rationale for experiments to be reported

As discussed in Chapter 1, there are two parietal lobe³ circuits involved in spatially directed/oriented behaviour these are referred to as the oculomotor and reaching neural circuits.

Neurones of the oculomotor circuit respond to visual stimuli whatever the distance of the stimuli from these neurones (Rizzolatti, 2002). They have receptive fields that code information in retinal coordinates and the motor properties of these neurones are exclusively related to eye movements (Anderson et al; 1997). Zipfer and Anderson (1988) showed that the position of an object is reconstructed by computing the position of the object's image on the retina and the position of the eye in the orbit.

In contrast, neurones of the reaching circuit comprise mostly bimodal neurones which respond to both tactile and visual stimuli. Receptive fields of neurones in the reaching circuit are anchored to the body parts to which they correspond regardless of eye or body part position (Gentilucci et al, 1983; 1988; Granziano and Gross, 1995). Neurones in the reaching circuit are activated by a stimulus presented within reach of the relevant body part regardless of its exact spatial position (Gentilucci et al, 1983; 1988; Granziano and Gross, 1995). Previc (1990a) proposed that the major role of the peripersonal (near) behavioural system was to reach for, grasp and manipulate objects manually. According to Previc (1990a) there are two components of the peripersonal (near) system: one that controls the movements of the arm and hand in reaching and grasping and one that programmes the oculomotor responses that assist in such movements.

The lesions studies and neuropsychological data reviewed in Chapter 1 seem to suggest that the areas that process information in near and far space are functionally distinct. However, patients with a dissociated performance between near and far space are the

³ The ocular motor circuit is formed by the lateral intraparietal area (LIP) and the frontal eye field (FEF). The reaching circuit is formed by the ventral intraparietal area (VIP) and the premotor area (F4) [Snyder et al, 1997; Rizzolatti et al. 1998; Colby and Goldberg, 1999].

exception rather than the rule. Although it is not entirely clear from the relevant reports, it would seem that the dissociation is not dichotomous but rather a matter of degree. From personal observation it is clear that patients showing this dissociated performance detect fewer targets in near/far than in far/near space rather than making no contralesional errors at all in near/far relative to many errors in near/far.

It has been suggested that PA training ameliorates left USN by “modifying visuomotor representations” (Angeli, Benassi and Ladavas, 2004). The original PA training regime described by Rossetti (1998) requires patients to adapt to the prismatic shift by pointing to objects in far space (beyond arm’s reach). This can be thought of as a far space PA treatment condition and will be referred to as ‘far space PA training’ in this thesis. However, the patients in Rossetti’s (1998) study were asked to perform tasks that evaluated the effects of PA (line bisection) **only** in **near** space. The findings showed that ‘far space PA training’ improved performance on a line bisection task in near space. Thus ‘far PA training’ ameliorated left USN performance in near space, at least for some patients.

The fact that ‘far PA training’ appears to ameliorate near space USN (Rossetti, 1998) suggests that a common underlying mechanism involved in both near and far space processing is ameliorated by PA. Serino, Bonifazi, Pierfederici and Ladavas (2008) argue that PA acts like a trigger that induces a leftward resetting of the oculomotor system. Indeed evidence has been presented that suggests the oculomotor system may be involved in far space and to some degree near space. To recapitulate:-

- a) neurones in the oculomotor system respond to visual stimuli whatever the distance of the stimuli from these neurones (Rizzotti and Berti, 2002) suggesting that the oculomotor system is involved in the detection of targets in near and in far space.
- b) Previc’s model (1995) postulates two components of the peripersonal (near) system: one that controls the movements of the arm and hand in reaching and

grasping and one that programmes the oculomotor responses that assist in such movements.

It would be of interest to explore whether a 'near' PA training procedure, which attempts to engage near/reaching circuits, would ameliorate USN in near and far space. As well as activating reaching/near circuits the near PA procedure may also activate far/oculomotor circuits as neurones of the oculomotor circuit have been shown to respond to visual stimuli whatever the distance of the stimuli from the observer (Rizzolatti, 2002). It was therefore reasoned that, if there is any benefit to modifying visuo-motor representation in the near/reaching circuits in addition to oculomotor circuits, near PA may reduce USN in near and far space but the effects may be greater in near space (due to the additional involvement of near/reaching circuits).

Alternatively, if PA works by ameliorating the oculomotor system activating near/reaching circuits may be irrelevant; consequently the effects of near PA training may actually be greater in far space. This is because even though oculomotor circuits may be involved in the detection of targets in both near and far space, the oculomotor system may play a greater role in the detection of targets in far space since lesions to the oculomotor circuit (LIP-FEF) in monkeys produce a preference for ipsilesional stimuli and, in cases of large lesions to the FEF, unawareness for the contralesional side of space, which is particularly marked in far space relative to near space.

3.2.2) What is the most appropriate near space PA training procedure?

One possibility is that the near PA training procedure should be very similar to the conventional (previously reported) far space procedure (Rossetti, 1998). Instead of requiring patients to respond to stimuli in far space (where they can not be reached), the stimuli would be placed within reaching distance (near space) and the patients would be asked to make a pointing response. However, Berti, Smania and Allport (2002) suggested that the activation of near and far space representations (and consequently the awareness for stimuli presented in different sectors of space) is not dependent solely upon the computation of the reaching distance but may, at least to some degree, be

modulated by the specific nature of the actions performed. Thus it is not clear that pointing to a stimulus in near space would elicit reaching-related activity in near space neural circuits. Conceivably, it is the intention to interact with the object, by grasping and reaching, that determines the activation of the reaching circuit. Furthermore, according to Previc's (1995) amalgamated model of 3D space, it is difficult to locate extrapersonal (far) space at any particular point within 3D space, because typically far space is centred on one's fixational or attentional plane. Consequently, it can shift from inside the outer boundary of peripersonal space to well beyond the limit of what Previc (1990a) refers to as the ambient extrapersonal realm (which can be located more than 30 metres from the viewer). It was therefore reasoned that the near space PA training procedure should incorporate the intention to reach, grasp and manipulate objects, since this is the major role of the peripersonal (near) behavioural system (Previc, 1995) and these actions would necessarily activate those circuits involved in reaching in near space (Berti, Smania and Allport, 2002).

The near space PA training used in the experiments to be reported therefore differed from the conventional far PA procedure (described by Rossetti, Rode, Pisella et al. 1998) in two important ways. Firstly, the stimuli were presented in near reaching space, as opposed to far space. Secondly, to ensure that near space representations were activated, patients were asked to grasp and manipulate objects (whilst wearing prism glasses) – actions that can only be carried out in near space (in contrast to pointing to objects which is an action that can be carried out whether the stimuli are in near or far space). The new procedure and the conventional procedure are similar in the following ways: In both the conventional far PA procedure and the near PA procedure to be described in the method section, patients receive visual feedback that they are pointing to the right of the stimulus or that they are mis-reaching for the stimulus. In both procedures patients must adjust their pointing/reaching trajectory in order to correctly point to (far PA) or grasp (near PA) the stimulus.

General methodology

The purpose of this section is to give general methodological details that apply to many of the studies reported in this thesis so as to avoid unnecessary repetition. This section will give details of the patients and control participants who took part in several of the experiments to be reported as well as details of the measures of USN (visual search task, three subtests from the BIT) which have been used in several of the experiments. Ways of treating the data to be reported in several experiments (e.g. visual search data) will also be stated in this section to avoid repeating this in each of the relevant experiments. Specific procedures and designs will be reported in the method sections of each experiment as well as reporting which of the nine patients (whose profiles are reported in this section) took part in each particular experiment.

3.3) Participants

The participant section will give details of all participants (patients and healthy controls) whose data featured in the experiments to be reported in this thesis.

3.3.1) Patients with USN: This thesis reports data from nine patients with USN. All patients gave informed consent before participating (see appendix one for an example of the consent form and patient information letter). The study was approved by the Dyfed Powys ethical committee (see appendix two). Patients were recruited from Swansea NHS trust. Research has suggested that spontaneous recovery of USN is unlikely after the patient has had USN for three months or longer (Ringman, Saver, Woolson, et al. 2004). Therefore, patients were only included in the study if they had had USN for three or more months. The mean age of the nine patients was 60.89 and the standard deviation was 20.72. The age range was 29 years to 90 years of age. Two of the patients were female and seven were male. All patients were right-handed. Each patients demographical, neuropsychological and neurological profiles can be seen below.

3.3.1.1) Patient JH

JH was a married lady who had left school at the age of 17 without formal qualifications. She had previously worked as a domestic, a sale assistant, and barmaid. JH suffered

from a deep right hemisphere haemorrhagic stroke at the age of 44 and was diagnosed with a rare brain condition called Moyamoya disease. The pathogenesis of Moyamoya disease is unknown. Moyamoya disease is characterized by progressive intracranial vascular stenoses of the circle of Willis resulting in successive ischaemic events. A CT scan taken three months prior to the start of this study showed damage to the right basal ganglia.

JH had left hemianopia (as determined by visual perimetry testing). Initially, JH had hemiparalysis of her left arm and leg, although during her involvement in this research (three months post stroke) she had regained some use of her arm and leg and was able to walk with a stick. Two months post stroke JH was given a neuropsychological assessment (by an assistant neuropsychologist working at the hospital) the details of which can be seen in Table 3.1.

Table 3.1 shows JH's neuropsychological profile two months post stroke.

Test name		Scores
Wechsler Test of Adult Reading:	Pre morbid IQ	90
Wechsler Adult Intelligence Scale-III	Verbal IQ	95
	Performance IQ	69
Wechsler Memory Scale-III:	Immediate recall	21 (Unimpaired)
	Delayed recall	25 (Unimpaired)
Short stories	Immediate recall	18 (Impaired)
	Delayed recall	20 (Impaired)
Family pictures	Star cancellation	Left USN (Left = 0/27; Right = 26/27)
	Letter cancellation	Left USN (Left 2/20; Right = 19/20)
	Line crossing	Left USN (Left = 0/18; Right = 16/18)
Birmingham Object Recognition Battery	Picture naming	72/76
Beck Depression Inventory ⁴		3/21 (No clinical depression)
Beck Anxiety Inventory ⁵		6/21 (Mild anxiety)

⁴ Beck, Steer and Brown (1996).

Neuropsychological testing took place two months after JH's stroke whereas JH was not asked to participate in this research until three months post stroke.

Neuropsychological assessment suggested that JH's post-stroke performance on the verbal subtests of the Wechsler Adult Intelligence Scale III⁶ (95) was consistent with her pre-morbid verbal IQ (90). Her performance IQ, however, was much lower post-stroke due to 'severe' left-sided USN (69). The patient's performance on the Wechsler Memory Scale⁷ (WMS) suggested that her verbal memory was unimpaired. Visual memory was impaired on the WMS because JH only reported information on the right-side of the pictures presented to her. JH correctly identified 72 of the 76 line drawings presented to her from the Birmingham Object Recognition Battery (BORB⁸) suggesting that her ability to recognise objects had not been comprised. JH's scores on three subtests of the Behavioural Inattention Test (BIT⁹) suggested that she was within the clinical range for USN as defined by the BIT manual (see appendix 3 for cut off scores).

3.3.1.2) Patient GR

GR was a 74 year old, married male. On leaving school he had obtained a degree in engineering and had worked as a civil engineer until the age of 65 when he retired. GR had required kidney dialysis four times a week since the age of 72. In 2006, GR had suffered a right hemispheric stroke, after which he was unable to use his left arm and leg. A MRI scan, taken three months prior to the start of this study, showed wide small wide spread areas of attenuation in the cerebral hemispheres and a right-sided thalamic anterior midbrain infarct. He consented to take part in this research three months post stroke; at this time he had not regained the use of the use of his left arm and leg. GR was seen in his own home. GR had not previously been given a full neuropsychological assessment but had been seen by an occupational therapist (OT) and given four subtests from the BIT and a line drawing test from the BORB.

⁵ Beck and Steer (1990)

⁶ Wechsler, D. (1997a)

⁷ Wechsler, D. (1997b)

⁸ Riddoch and Humphreys, (1993)

⁹ Wilson, Cockburn and Halligan (1987a)

Table 3.2: GR's neuropsychological profile.

Test Name	Subtests	Scores
BIT	Star cancellation	Left USN (Left = 2/27; Right = 25/27)
	Letter cancellation	Left USN (Left 0/20; Right = 18/20)
	Line crossing	Left USN (Left = 1/18; Right = 15/18)
BORB	Picture naming	73/76

GR did not appear to have difficulty with identifying line drawings but show marked USN on three BIT subtests. His scores on each of the three BIT subtests were within the clinical range of USN as defined by the BIT manual. His wife reported that GR often neglected people who stood to his left and sometimes missed items and food on the left side of his plate and objects located to his left such as the television remote control.

3.3.1.3) Patient PC

PC was a married retired nurse. At the age of 69 PC suffered a right cerebral hemispheric stroke. A CT scan taken three months prior to the start of this study showed a right frontal-parietal lesion and damage to white matter around the right anterior centrum semiovale. After her stroke the patient experienced left hemiparalysis and left hemianopia (revealed by visual perimetry testing). Two months post stroke she was seen by a clinical neuropsychologist for assessment; summarised details of this assessment can be seen in Table 3.3.

Table 3.3 shows PC's neuropsychological profile two months post stroke.

Test name	Scores
Wechsler Test of Adult Reading:	Pre-morbid IQ 92
WAIS-III	Verbal IQ 91
	Performance IQ 69
WMS-III: Short stories	Immediate recall 22 (Unimpaired)
	Delayed recall 17 (Unimpaired)
WMS-III: Designs	Immediate recall 18 (Unimpaired)
	Delayed recall 12 (Impaired)
BIT	Star cancellation Left USN (Left = 3/27; Right = 26/27)
	Letter cancellation Left USN (Left 2/20; Right = 17/20)
	Line crossing Left USN (Left = 3/18; Right = 17/18)
BORB	Picture naming 75/76

** Neuropsychological testing took place two months after PC's stroke whereas PC was not asked to participate in this research until three months post stroke.*

Neuropsychological assessment suggested that PC's post-stroke performance on the verbal subtests of the Wechsler Adult Intelligence Scale III (91) was consistent with her pre-morbid verbal IQ (92). Her performance IQ, however, was much lower post-stroke due to a left-sided USN (69). PC's performance on the Wechsler Memory Scale (WMS) suggested that her verbal memory was unimpaired. Immediate visual memory recall was unimpaired whereas delay visual memory recall was impaired (as defined by the WMS manual). PC correctly identified 75 of the 76 line drawings presenting to her suggesting that her ability to recognise objects had not been comprised. PC's scores on four subtests of the BIT suggested that her performance was in the clinical range for USN as defined by the BIT manual.

Three months post stroke PC consented to take part in this research, at this time she had not regained function in her left arm or leg and was confined to a wheel chair throughout her involvement in the study. For the first 5 months of the study PC was seen in a quiet room of the rehabilitation hospital where she was staying. PC was then moved to a residential home and she seen in her sitting room for the remainder of the investigation.

3.3.1.4) Patient RG

RG was a 44 year old married man, with two daughters both of whom had left home. He left school without any formal qualifications and had then trained as a fireman. RG had taken early retirement due to arthritis. He suffered an extensive right middle cerebral infarct in 2006. The CT scan showed an extensive right temporal frontal parietal lesion. After the stroke RG experienced left hemiparalysis and left USN (as determined by clinical observation of ward staff). RG also had hemianopia as determined by perimetry testing. RG was seen for neuropsychological testing three months post stroke by a trainee clinical psychologist. A summary of this assessment can be seen in Table 3.4.

Table 3.4 shows RG's neuropsychological profile three months post stroke.

Test name		Scores
Wechsler Test of Adult Reading:	Premorbid IQ	89
WAIS-III	Verbal IQ	97
	Performance IQ	65
WMS-III: Short stories	Immediate recall	11 (Unimpaired)
	Delayed recall	9 (Unimpaired)
WMS-III: Family pictures	Immediate recall	5 (Impaired)
	Delayed recall	2 (Impaired)
BIT	Star cancellation	Left USN (Left = 1/27; Right = 13/27)
	Letter cancellation	Left USN (Left 0/20 left; Right = 5/20)
	Line crossing	Left USN (Left = 0/18; Right = 16/18)
VOSP	Number location	6/10 (Impaired)
	Object decision	17/20 (Unimpaired)
BDI (Fast Screen)		0/21 (no clinical depression)
HADS		3/21 (no clinical anxiety)

** Neuropsychological testing took place three months after RG's stroke just prior to his involvement in the research reported in this thesis.*

This neuropsychological testing occurred just before RG was given PA training. RG was given PA training in a rehabilitation ward (in a primary care hospital). Three months later he was discharged from hospital to his own home, following up testing was therefore conducted in his own home. RG was confined to a wheelchair throughout his involvement in this research study.

3.3.1.5). Patient LT

LT was a 45 year old, divorced male. He left school without any formal qualifications and had previously worked as a machine operator, a driver and a delivery man. LT suffered a stroke after a rupture of a right middle cerebral artery aneurysm necessitating evacuation of a right subdural haematoma. A CT scan, taken four months prior to the start of this study, showed a large right-sided lesion involving the frontal-parietal-temporal lobe. The patient had left-hemiparalysis, left hemianopia (as determined by visual perimetry testing) and left USN (determined by clinical observation of ward staff). LT was given a neuropsychological assessment two and a half months post stroke

by a consultant neuropsychologist. At this time the patient reported having blurred vision in his right eye (confirmed by visual acuity testing) and thus it was not possible to assess non verbal intellect, memory or visuo-spatial abilities using formal cognitive assessment. The neuropsychologist reported that LT appeared to have left USN because, when visual acuity was being tested, he only reported words on the right-side of pages (or the right half of longer words). The neuropsychological report also suggested that LT may have been socially disinhibited (disclosing very personal information) and had attentional difficulties (he did not respond to verbal interruptions). Details of the limited neuropsychological data obtained in this neuropsychological assessment can be seen in Table 3.5. Just prior to taken part in the study LT was re-tested for visual acuity; the test showed no visual problems due to blurred vision in his right eye. LT was then given three subtests from the BIT and a picture naming test from the BORB. The results both assessments can be seen in Table 3.5.

Table 3.5: LT's neuropsychological profile.

Test		Scores
Wechsler Test of Adult Reading:	Premorbid IQ	80
WAIS-III	Verbal IQ	80
	Performance IQ	Not tested
WMS-III Short stories	Immediate recall	Unimpaired
	Delayed recall	Unimpaired
BIT	Star cancellation	Left USN (Left = 3/27; Right = 20/27)
	Letter cancellation	Left USN (Left 6/20 left; Right = 18/20)
	Line crossing	Left USN (Left = 0/18; Right = 16/18)
BORB	Picture naming	65/76
BDI		6/21 (mild depression)
BAI		10/21 (mild anxiety)

LT's verbal IQ (80) was consistent with an estimate of his premorbid IQ (80). LT's verbal memory (immediate and delayed) was unimpaired as assessed by the short stories tests from the WMS. Score from three subtests from the BIT battery showed that LT had left USN (as defined by the BIT manual – see appendix 3). Picture naming was unimpaired. LT consented to take part in this research four months after his stroke and

was seen in his own home. LT regained some function in his left arm and leg during his involvement in the study.

3.3.1.6) Patient JB: JB was a 74 year old retired male. JB suffered from a stroke after which he presented with left USN (as determined by behaviour observed by her physiotherapist), left hemianopia (as determined by visual perimetry testing) and a mild hemiplegia affecting his left arm; he had regained the use of his left leg and was able to walk with a stick. CT scans showed right superior occipital damage (Brodmann's areas 18 and 19) and damage to the right parietal lobule (Brodmann's area 7). The patient consented to take part in the treatment programme three month post stroke. He was referred by a physiotherapist because he appeared to be unaware of people standing to his left and when asked to pick up rubber rings and place them on three vertical sticks presented to his left, midline and right he failed to detect the stick in his left visual field. The physiotherapist also reported that he would often walk into objects on his left.

3.3.1.7) Patient EI: EI was a 90 year old married male. The patient presented with a left hemianopia, visual neglect and hemiplegia, the patient had regained the use of his left leg and was able to walk with a frame during his involvement in the study. A CT scan showed cortical and subcortical damage to the right occipital lobule (Brodmann's areas 37 and 19), cutting across the optic radiations. EI was referred to this study by a physiotherapist and OT working in an older adult community rehabilitation setting. EI had been discharged from hospital and was living in his own home with support from his wife and paid carers. He had suffered a stroke 5 months before being invited to take part in this research. Case notes stated that visual perimetry testing had indicated a left hemianopia.

3.3.1.8) Patient DH: DH was a 65 year old male who had suffered a right hemisphere haemorrhagic stroke. DH was hospitalised for two months after his stroke before being discharged to his own home. DH had heard about the study from a friend of his family who had worked in a local rehabilitation hospital. This lady contacted the experimenter and asked if DH could be involved in the study. DH was seen in his own home 4 months

post stroke. Shortly after PA training DH moved out of the area to live with his daughter. CT scan and previous neuropsychological data were unavailable for this patient. However, after giving consent to take part in the study, DH was given three subtests from the BIT to confirm a diagnosis of USN. A summary of the data can be seen in Table 3.6.

Table 3.6: Scores obtained by DH immediately after consenting to take part in the study on three BIT subtests

Test	Subtests	Scores
BIT	Star cancellation	Left USN (Left = 9/27; Right = 23/27)
	Letter cancellation	Left USN (Left 12/20 left; Right = 20/20)
	Line crossing	Left USN (Left = 11/18; Right = 18/18)

Scores of all three subtests of the BIT were within the clinical range for USN as defined by the BIT manual (see appendix 3).

3.3.1.9) Patient RB: RB was a 28 year old male. The patient presented with a left hemianopia and left-sided USN after a (self inflicted) air gun wound to the head. RB's CT scan showed damage to the right anterior temporal lobe (cortical and subcortical) and damage to the right posterior inferior frontal white matter. RB was seen by a neuropsychologist three months after being admitted to hospital. A summary of the details of the assessment can be seen in Table 3.7. Visual subtests of the WAIS and WMS were not administered due to RB's left-sided USN.

Table 3.7: RB's neuropsychological profile.

WAIS	Vocabulary	Unimpaired
	Arithmetic	Unimpaired
	Digit span	Unimpaired
WMS	Logical memory immediate	Unimpaired
	Logical memory delayed	Unimpaired
	Verbal paired associates immediate	Unimpaired
	Verbal paired associates delayed	Unimpaired
BIT	Star cancellation	Left USN (Left = 5/27; Right = 24/27)
	Letter cancellation	Left USN (Left 2/20 left; Right = 17/20)
	Line crossing	Left USN (Left = 4/18; Right = 18/18)

Scores on Immediate and delayed verbal memory subtests from the WMS indicated that RB was in the average range and that he was able to retain verbal information after a 30 minute delay. RB's arithmetic and digit span scores suggest that his working memory was not impaired. Scores on three subtests of the BIT suggested that RB had a left-sided USN as defined by the BIT manual (see appendix 3 for cut off scores). During the neuropsychological examination RB was presented with 30 simple line drawings of objects taken from the Snodgrass and Vanderwart collection (1980). He was able to correctly name all of these objects suggesting that his ability to recognise objects had not been comprised. The neuropsychologist reported that RB had poor executive function with poor initiation and motivation (however, evidence for this was not formally assessed).

The patient was approached to take part in this investigation 7 months after his accident. He was referred by a neuropsychologist working in a traumatic brain injury unit. RB had been discharged from hospital and was living in his own home with live-in carers at the time of the study. RB was able to walk and had limited use of his left arm. RB often collided with objects on his left hand side.

Table 3.8 summarises the clinical and neurological details of the patients with USN who participated in the experiments to be reported in this thesis.

Table 3.8: Clinical details of the nine patients with USN who participated in the experiments to be reported in this thesis

Patient	Age	Sex	Cause of brain damage	Lesion details	Time since brain injury	Hemiparesis	Hemianopia	USN
1) JH	44	F	Moyamoya disease. Haemorrhagic stroke	CT scan showed damage to the right basal ganglia	3 months	Present initially but most function regained over testing period	Present	Present
2) GR	74	M	Ischaemic Stroke	MRI scan showed wide spread small areas of high attenuation of the cerebral hemispheres and a right-sided thalamic midbrain infarct.	3 months	Present	Absent	Present
3) PC	69	F	Ischaemic stroke	CT scan showed a lesion of the right frontal-parietal lobe (including white matter damage around the anterior centrum semiovale)	3 months	Present	Present	Present
4) RG	44	M	Haemorrhagic stroke	CT scan showed damage to the right temporal, frontal and parietal regions	3 months	Present	Present	Present
5) LT	45	M	Ischaemic stroke: rupture of the right middle cerebral artery	CT scan showed a right frontal-temporal-parietal lesion (damage to the basal ganglia, putamen and insula, superior and anterior damage to the right temporal lobe and a slight frontal lesion).	4 months	Present initially but some function regained over testing period	Absent	Present
6) JB	74	M	Haemorrhagic stroke	CT scan showed damage to the right superior occipital lobe (BA 18 & 19). Damage to the right posterior parietal lobe (BA, 7). Damage to the periventricular white matter	3 months	Present initially but some function regained over testing period	Present	Present
7) EI	90	M	Haemorrhagic stroke	CT scan showed cortical and subcortical damage to the right occipital lobe (BA, 37 & 39) cutting across the optic radiations	5 months	Present initially but some function regained over testing period	Present	Present
8) DH	65	M	Haemorrhagic stroke	CT scan not available	4 months	Present	Present	Present
9) RB	28	M	Gun shot wound	CT scan showed cortical and subcortical damage to the right anterior temporal lobe and damage to the posterior inferior frontal white matter	7 months	Present initially but some function regained over testing period	Present	Present

3.3.2) Control participants

Ten right-handed healthy age matched control participants consented to take part in this research. All participants had normal or corrected to normal vision.

The mean age of the sample was 89 and the standard deviation 17.78. The age range of the sample was 33 years old to 89 years old. Seven of the participants were carers or spouses of the patients with USN. Three participants were (two were technical support staff and the other administration staff) member of staff working at Swansea University. Five of the control participants were female and the remaining five were male.

3.4) Measures of USN and administration procedures

The presence of USN was confirmed for each patient using three subtests from the standardised Behavioural Inattention Test (BIT) after the patients had consented to take part in the study. If a patient scored below the normal cut off point on three of the BIT subtests they were included in the study. USN was also assessed using a visual search task. (the BIT data and visual search data obtained after patients had consented to take part in the study made up the data to be reported in this thesis). In order to be included in the research patients had to exhibit a clear gradient in search times favouring ipsilesional over more contralesional targets on at least one of the two visual search tasks. Each measure of USN (BIT subtests and the visual search task) will be discussed in detailed below.

3.4.1) Measures of USN: visual search task

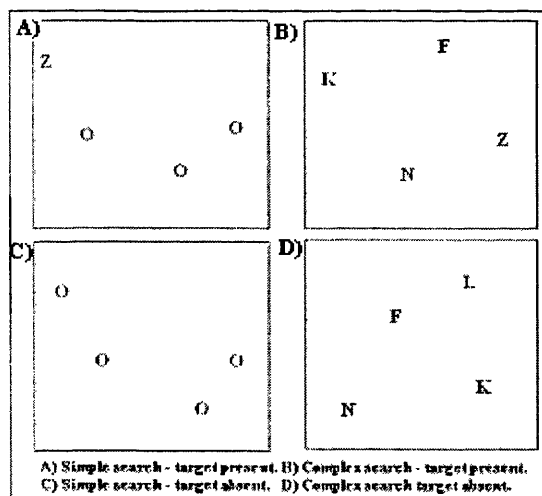
Participants¹⁰ were given a computerised visual search task. The test was run on a 15 inch wide screen laptop (Dell Inspiron 8500). The program was written using QNX. Participants were asked to search the screen for the target letter 'Z'. They responded by pressing a key labelled 'YES' and 'NO'. Labels were placed on the arrow keyboard keys. The 'up' arrow was labelled 'YES' and the 'down' arrow was labelled 'NO' for half of the participants. For the remaining participants the 'up' arrow was labelled 'NO'

¹⁰ The term participant will be used in this thesis when describing measures used by both patients with USN and healthy control participants.

and the down arrow 'YES'. In the presence of two keys, patients with USN may show a response bias to the rightmost key. The up and down arrow keys were chosen as the up arrow is located above the down arrow and so eliminated a 'rightward' response bias.

The stimuli consisted of different letters of the alphabet. The target letter was the letter 'Z'. The target always appeared with distractor letters. The number of distractors varied from 2 to 8, 16 or 32. There were two types of trials; simple feature trials and complex feature trials. On simple feature trials distractors were always the letter 'O' (the letter 'Z' appearing to pop out); on complex feature trials other letters of the alphabet (N, K, H, R etc) were used. The distractor letters for complex trials were chosen because they shared similar features to the letter 'Z' (straight lines). See Figure 3.1 for an example of the stimuli used in both simple (a, c) and complex (b, d) conditions.

Figure 3.1: An example of the stimuli used in simple and complex searches.



There were 96 trials for which the target letter 'Z' was present and 96 trials for which the target letter 'Z' was not present: target absent trials (192 trials in total).

For target present trials, the target could appear at one of seven different positions across the X axis; far left, mid left, left (nearest to the midline), midline, right (nearest to the midline), mid-right and far right, and at one of seven positions along the Y axis. Of the

target present trials, 48 were simple trials and the remaining 48 were complex trials. Of the 48 simple trials 12 target present trials were presented with 2 distractors, 12 with 8 distractors, 12 with 16 distractors and 12 with 32 distractors. Of the 48 complex search trials 12 target present trials were presented with 2 distractors, 12 with 8 distractors, 12 with 16 distractors and 12 with 32 distractors. Figure 3.2 shows the X (horizontal) and Y (vertical) co-ordinates of the targets.

Figure 3.2: Possible positions at which the targets could appear.

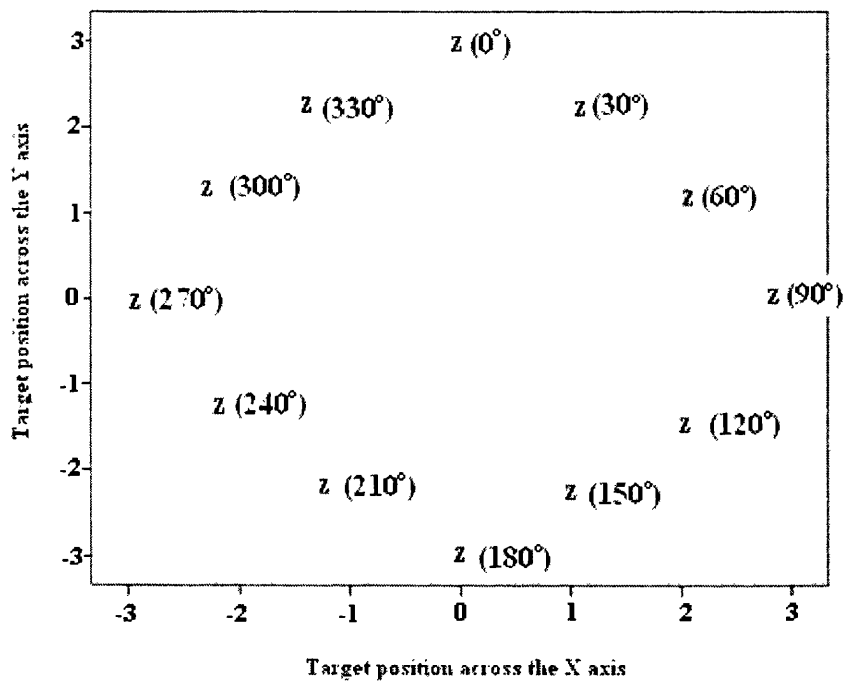


Figure 3.2 shows the 12 possible positions that the target letter 'Z' could appear on the X and Y axis. Each target appeared eight times in the positions indicated in Figure 3.2. Far left targets (X-axis -3, Y axis 0) and far right targets (X-axis 3, Y axis 0) appeared eight times in total. The rest of the target positions across the X axis occupied two positions on the Y-axis. For example the midline targets could appear at the upper or lower half of the computer screen (X axis 0, Y axis 3) or (X axis 0, Y axis -3). Therefore the target was presented 16 times at all target positions on the X axis, with the exception of far left and right positions, eight times to the upper half of the screen and eight times to the lower half of the screen.

At the far right and far left positions, four of the trials were simple search trials in which the target appeared with, 2, 8, 16 or 32 distractors. The remaining four trials were complex feature trials in which the target appeared with 2, 8, 16 or 32 distractors. At the remaining target positions, the target appeared twice as many times (16 times) because the target could appear in two positions on the Y-axis (but at the same position on the X-axis). Thus the target appeared at the upper half of the screen at the midline position eight times. Four of these trials were simple search trials in which the target appeared with 2, 8, 16 or 32 distractors. The remaining four trials were complex feature trials in which the target appeared with 2, 8, 16 or 32 distractors. The target would also appear at the lower half of the computer screen eight times. Four of the trials were simple search trials in which the target appeared with either 2, 4, 6 or 8 distractors. The remaining four trials were complex feature trials in which the target appeared with, two, eight, 16 or 32 distractors. Table 3.3 shows the number of targets presented at each target position on the X axis as a function of search type and set size.

Table 3.3 shows the number of targets presented at each target position on the X axis as a function of search type and set size.

Search type	No. of distractors	Far left (-3)	Mid left (-2)	Left (-1)	Midline (0)	Right (1)	Mid right (-2)	Far right (-3)	Total summed over target position
Simple	2	1	2	2	2	2	2	1	12
	8	1	2	2	2	2	2	1	12
	16	1	2	2	2	2	2	1	12
	32	1	2	2	2	2	2	1	12
Complex	2	1	2	2	2	2	2	1	12
	8	1	2	2	2	2	2	1	12
	16	1	2	2	2	2	2	1	12
	32	1	2	2	2	2	2	1	12
Total summed over set size		8	16	16	16	16	16	8	Total number of target present trial = 96

The order of stimulus presentation was randomly generated by QNX but this random order was the same order for each participant given the test. Simple and complex trials were presented within the same testing block in a randomised order.

When the visual search task was given in near space the laptop computer was positioned on a table in front of the patient, so that the screen was 57cm away from the patient's eyes. At a distance of 57cm, a one cm target on the screen subtends one degree of visual angle at the retina. When the visual search task was given in far space the laptop was positioned in the same place so that the patient could use the keys to respond. However, the screen was turned off and the patient was asked to look at the screen projected on the wall (via an LCD projector). The projected screen was 228 cm away from the patient's eyes. At this distance a one cm target on the screen would also subtend one degree of visual angle at the retina. The target and distractor letters would therefore subtended one degree of visual angle at the retina for both near and far space assessments. That is, the size of the image projected onto the retina was the same in near and far assessments. Participants were always instructed that a letter 'Z' could appear on the screen/wall and that his/her task was to respond to the letter 'Z' as quickly and as accurately as possible, by pressing the 'yes' key when the target was seen and the 'no' key when the target was not seen. The visual search task was presented in unlimited time.

3.4.2) Measures of USN: Behavioural Inattention Test (BIT)

Subtests from the Behavioural Inattention Battery (Wilson, Cockburn and Halligan, 1987a) were used to assess USN because a) these tests have been standardised on a group of 80 stroke patients and 50 controls; b) Inter-rater reliability (Pearson $r=.99$, $P<.001$, $n=13$) and c) test-retest reliability (Pearson $r=.99$, $P<.001$, $n=10$) are high (Wilson, Cockburn and Halligan, 1987b).

The BIT is comprised of 15 subtests; six conventional subtests and nine behavioural subtests. The BIT was standardised on a group of 80 stroke patients. 50 aged matched non brain damaged control participants were also assessed on the BIT battery to provide normative data for the test items. Table 3.4 provides demographic details of the patients and control group with whom the BIT battery was standardised and 'normed' against.